10/813745

Connecting via Winsock to STN

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:41:08 ON 24 JAN 2007

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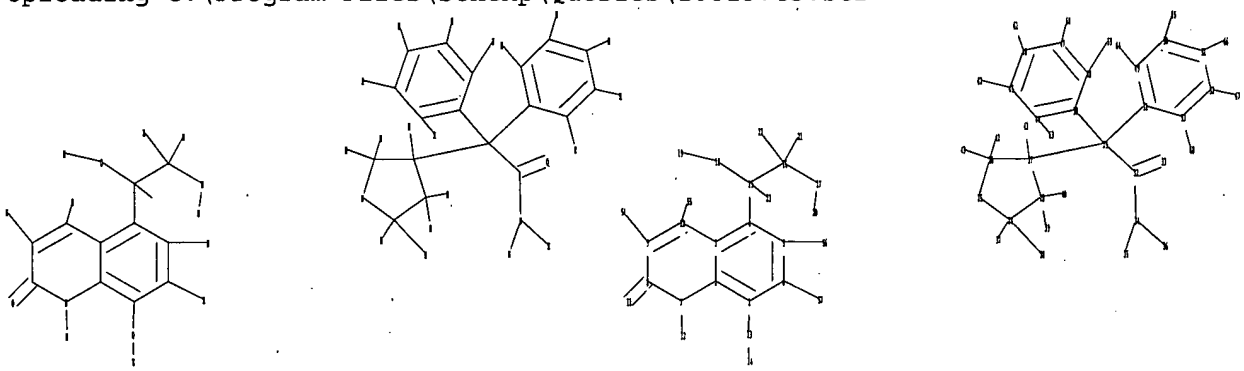

chain nodes :
11 12 13 14 15 16 17 18 19 20 21 22 23 29 32 33 34 35 36 37 38
39 40 41 42 43 54 55 56 57 59 60 61 62 63 64 65 66 67 68
ring nodes :
1 2 3 4 5 6 7 8 9 10 24 25 26 27 28 30 31 44 45 46 47 48 49
50 51 52 53
chain bonds :
1-13 4-15 5-56 6-57 7-12 8-11 9-54 10-55 13-14 15-16 15-18 15-23 16-17
16-21 16-22 17-20 18-19 24-37 24-38 26-42 26-43 27-29 27-41 28-39 28-40
29-30 29-31 29-32 32-33 32-34 34-35 34-36 44-63 45-62 46-61 47-60 48-59
49-64 50-65 51-66 52-67 53-68
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 24-25 24-28 25-26 26-27
27-28 30-44 30-48 31-49 31-53 44-45 45-46 46-47 47-48 49-50 50-51 51-52
52-53
exact/norm bonds :

```
1-13  2-7  3-10  7-8  8-9  8-11  9-10  15-18  16-17  24-25  24-28  25-26  26-27
27-28  32-33  32-34
exact bonds :
4-15  5-56  6-57  7-12  9-54  10-55  13-14  15-16  15-23  16-21  16-22  17-20
18-19  24-37  24-38  26-42  26-43  27-29  27-41  28-39  28-40  29-30  29-31  29-32
34-35  34-36  44-63  45-62  46-61  47-60  48-59  49-64  50-65  51-66  52-67  53-68
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  30-44  30-48  31-49  31-53  44-45  45-46  46-47
47-48  49-50  50-51  51-52  52-53
isolated ring systems :
containing 1 : 30 : 31 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS
19:CLASS  20:CLASS  21:CLASS  22:CLASS  23:CLASS  24:Atom  25:Atom  26:Atom
27:Atom  28:Atom  29:CLASS  30:Atom  31:Atom  32:CLASS  33:CLASS  34:CLASS
35:CLASS  36:CLASS  37:CLASS  38:CLASS  39:CLASS  40:CLASS  41:CLASS  42:CLASS
43:CLASS  44:Atom  45:Atom  46:Atom  47:Atom  48:Atom  49:Atom  50:Atom  51:Atom
52:Atom  53:Atom  54:CLASS  55:CLASS  56:CLASS  57:CLASS  59:CLASS  60:CLASS
61:CLASS  62:CLASS  63:CLASS  64:CLASS  65:CLASS  66:CLASS  67:CLASS  68:CLASS



L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


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FULL SCREEN SEARCH COMPLETED -        1 TO ITERATE

100.0% PROCESSED        1 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

L3            0 SEA SSS FUL L1

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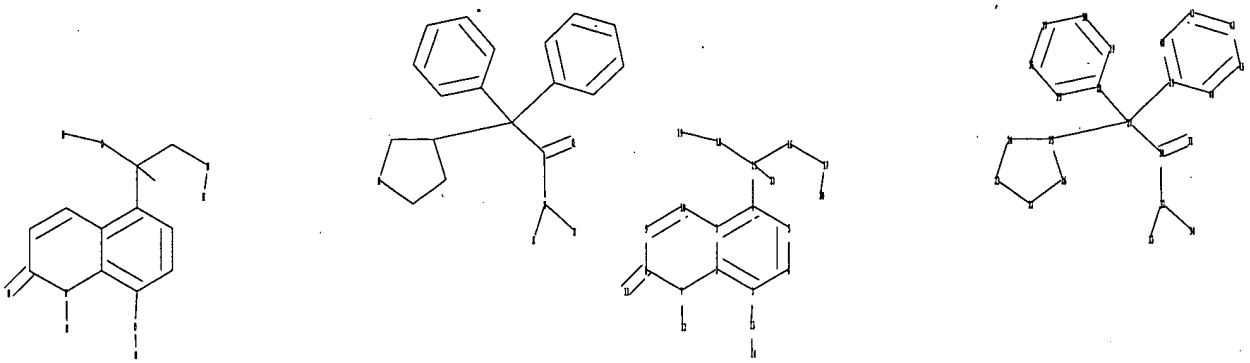

chain nodes :
11 12 13 14 15 16 17 18 19 20 21 27 30 31 32 33 34
ring nodes :
1 2 3 4 5 6 7 8 9 10 22 23 24 25 26 28 29 35 36 37 38 39 40
41 42 43 44
chain bonds :
1-13 4-15 7-12 8-11 13-14 15-16 15-18 15-21 16-17 17-20 18-19 25-27
27-28 27-29 27-30 30-31 30-32 32-33 32-34
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 22-23 22-26 23-24 24-25
25-26 28-35 28-39 29-40 29-44 35-36 36-37 37-38 38-39 40-41 41-42 42-43
43-44
exact/norm bonds :
1-13 2-7 3-10 7-8 8-9 8-11 9-10 15-18 16-17 22-23 23-24 30-31 30-32
exact bonds :
4-15 7-12 13-14 15-16 15-21 17-20 18-19 22-26 24-25 25-26 25-27 27-28
27-29 27-30 32-33 32-34
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 28-35 28-39 29-40 29-44 35-36 36-37 37-38
38-39 40-41 41-42 42-43 43-44
isolated ring systems :
containing 1 : 22 : 28 : 29 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:CLASS
28:Atom 29:Atom 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:CLASS 35:Atom
36:Atom 37:Atom 38:Atom 39:Atom 40:Atom 41:Atom 42:Atom 43:Atom 44:Atom

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

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FULL SCREEN SEARCH COMPLETED - 4 TO ITERATE

100.0% PROCESSED 4 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L5 0 SEA SSS FUL L4

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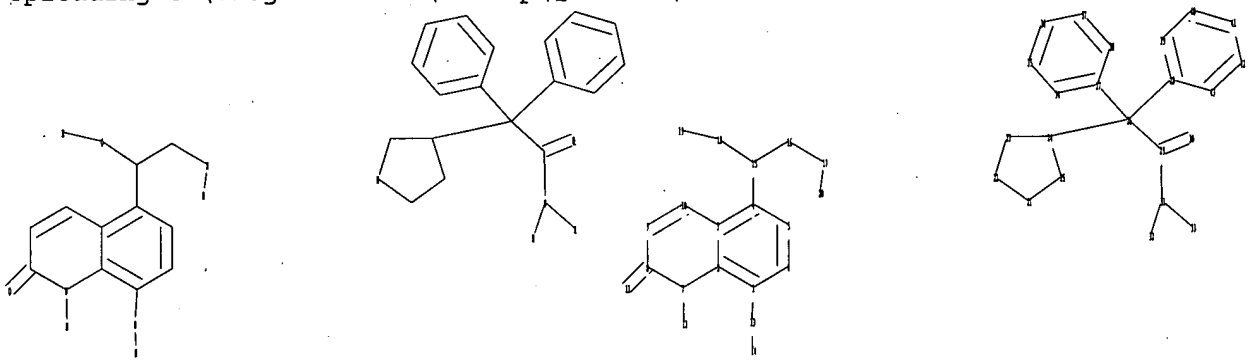

chain nodes :
11 12 13 14 15 16 17 18 19 20 26 29 30 31 32 33
ring nodes :
1 2 3 4 5 6 7 8 9 10 21 22 23 24 25 27 28 34 35 36 37 38 39 40 41 42 43
chain bonds :
1-13 4-15 7-12 8-11 13-14 15-16 15-18 16-17 17-20 18-19 24-26 26-27 26-28 26-29 29-30 29-31 31-32 31-33
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 21-22 21-25 22-23 23-24 24-25 27-34 27-38 28-39 28-43 34-35 35-36 36-37 37-38 39-40 40-41 41-42 42-43

exact/norm bonds :
1-13 2-7 3-10 7-8 8-9 8-11 9-10 15-18 16-17 21-22 22-23 29-30 29-31
exact bonds :
4-15 7-12 13-14 15-16 17-20 18-19 21-25 23-24 24-25 24-26 26-27 26-28
26-29 31-32 31-33
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 27-34 27-38 28-39 28-43 34-35 35-36 36-37
37-38 39-40 40-41 41-42 42-43
isolated ring systems :
containing 1 : 21 : 27 : 28 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 27:Atom
28:Atom 29:CLASS 30:CLASS 31:CLASS 32:CLASS 33:CLASS 34:Atom 35:Atom
36:Atom 37:Atom 38:Atom 39:Atom 40:Atom 41:Atom 42:Atom 43:Atom

L6 STRUCTURE UPLOADED

=> d l6
L6 HAS NO ANSWERS
L6 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s l6 full
FULL SEARCH INITIATED 12:44:11 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 167 TO ITERATE

100.0% PROCESSED 167 ITERATIONS 146 ANSWERS
SEARCH TIME: 00.00.01

L7 146 SEA SSS FUL L6

=> file ca

=> s l7
L8 1 L7

=> d ibib abs fhitstr

L8 ANSWER 1 OF 1 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:350030 CA
TITLE: Preparation of (diphenyl)(pyrrolidinyl)methyl amides as β2 adrenergic receptor agonist and muscarinic receptor antagonist
INVENTOR(S): Mammen, Mathai; Hughes, Adam
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: PCT Int. Appl., 175 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
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WO 2004089892	A3	20041209			
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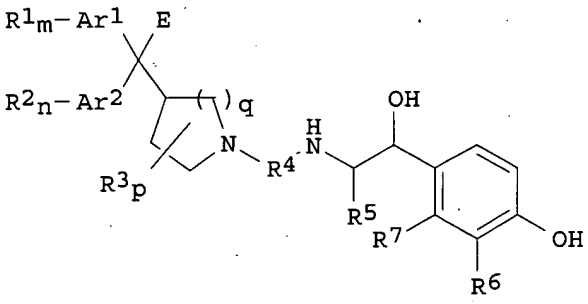
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1615881	A2	20060118	EP 2004-758642		20040331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK					
JP 2006522134	T	20060928	JP 2006-509589		20040331
US 2006287369	A1	20061221	US 2004-813745		20040331
PRIORITY APPLN. INFO.:			US 2003-459291P	P	20030401
			WO 2004-US9825	W	20040331

OTHER SOURCE(S): MARPAT 141:350030
GI



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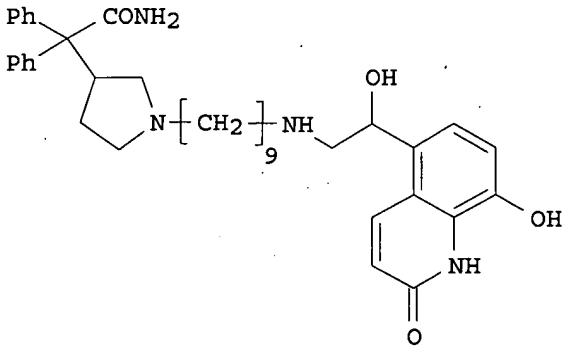


II

AB Title compds. represented by the formula I [wherein Ar1, Ar2 = independently Ph, (cyclo)alkyl, (un)substituted heteroaryl, heterocyclyl;

m = 0-3; n = 0-3; R1-R3 = independently (cyclo)alkyl, alkenyl, alkynyl, cyano, etc.; E = CN, OH, carbonylamino, carboxylate; p = 0-4; R4 = a divalent; R5 = H or alkyl; R6 = carbamoyl or alkoxyalkyl; R7 = H or R6R7 = (un)substituted (hetero)cyclyl; q = 1-2; and pharmaceutically acceptable salts, solvates or stereoisomers thereof] were prepared as β2 adrenergic receptor agonist and muscarinic receptor antagonist. For example, II was given in a multi-step synthesis starting from the reaction of (S)-1-benzyl-3-pyrrolidinol with p-toluenesulfonyl chloride. II was tested for radioligand binding at human β1, β2 and β3 adrenergic receptors with a ration of Ki(β1)/Ki(β2) greater than 8, and with Ki values of less than 50 nM at human muscarinic receptors, etc. Thus, I and their pharmaceutical compns. are useful as β2 adrenergic receptor agonist and muscarinic receptor antagonist for the treatment of pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

IT 777064-13-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (diphenyl)(pyrrolidinyl)methyl amides as β2 adrenergic receptor agonist and muscarinic receptor antagonist)

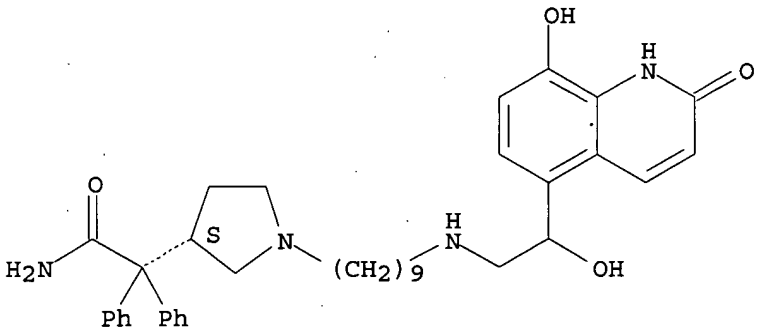
RN 777064-13-8 CA

CN 3-Pyrrolidineacetamide, 1-[9-[[2-(1,2-dihydro-8-hydroxy-2-oxo-5-quinolinyl)-2-hydroxyethyl]amino]nonyl]-α,α-diphenyl-, (3S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

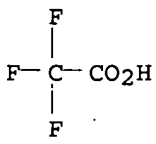
CRN 777064-12-7
CMF C38 H48 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



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=> s l6 full
L9            2 SEA SSS FUL L6

=> s l9/com
L10           1 L9/COM

=> d ibib abs fqhit

L10  ANSWER 1 OF 1  MARPAT  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         141:350030  MARPAT
TITLE:                    Preparation of (diphenyl)(pyrrolidinyl)methyl amides
                          as β2 adrenergic receptor agonist and muscarinic
                          receptor antagonist
INVENTOR(S):              Mammen, Mathai; Hughes, Adam
PATENT ASSIGNEE(S):       Theravance, Inc., USA
SOURCE:                   PCT Int. Appl., 175 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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     WO 2004089892      A3   20041209
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
             BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
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             TD, TG
     EP 1615881         A2   20060118       EP 2004-758642    20040331
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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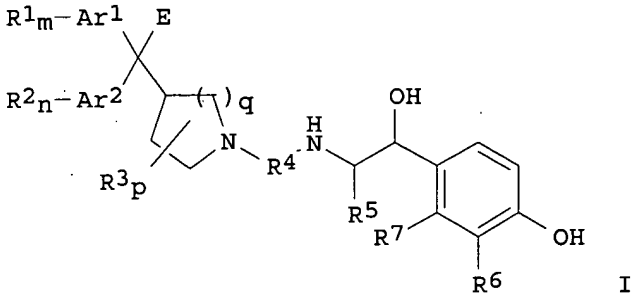

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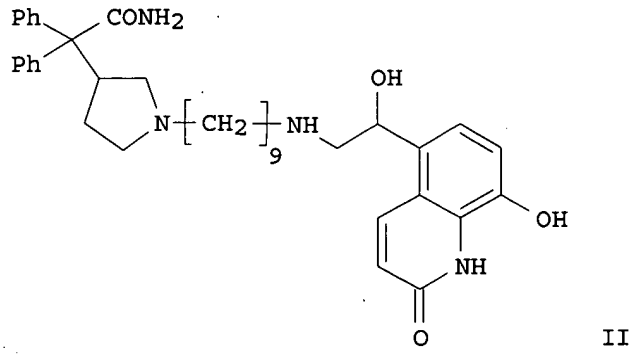
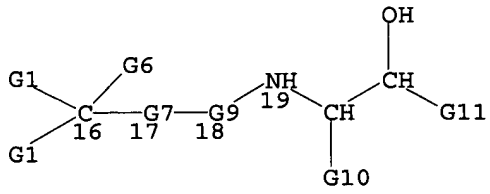


II

AB Title compds. represented by the formula I [wherein Ar1, Ar2 = independently Ph, (cyclo)alkyl, (un)substituted heteroaryl, heterocyclyl; m = 0-3; n = 0-3; R1-R3 = independently (cyclo)alkyl, alkenyl, alkynyl, cyano, etc.; E = CN, OH, carbonylamino, carboxylate; p = 0-4; R4 = a divalent; R5 = H or alkyl; R6 = carbamoyl or alkoxyalkyl; R7 = H or R6R7 = (un)substituted (hetero)cyclyl; q = 1-2; and pharmaceutically acceptable salts, solvates or stereoisomers thereof] were prepared as β2 adrenergic receptor agonist and muscarinic receptor antagonist. For example, II was given in a multi-step synthesis starting from the reaction of (S)-1-benzyl-3-pyrrolidinol with p-toluenesulfonyl chloride. II was tested for radioligand binding at human β1, β2 and β3 adrenergic receptors with a ration of Ki(β1)/Ki(β2) greater than 8, and with Ki values of less than 50 nM at human muscarinic receptors, etc. Thus, I and their pharmaceutical compns. are useful as β2 adrenergic receptor agonist and muscarinic receptor antagonist for the treatment of pulmonary disorders, such as chronic obstructive pulmonary disease and asthma.

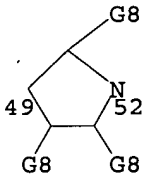
MSTR 1A



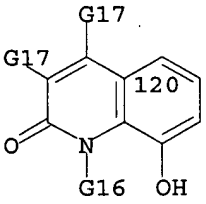
G1 = Ph (opt. substd. by (1-3) G2)
G6 = 31

31 C(O)-G33

G7 = 49-16 52-18



G11 = 120

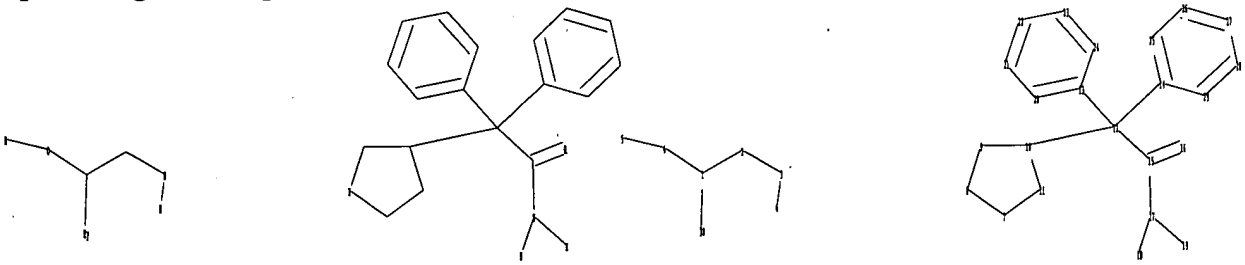


G33 = NH2

Patent location:	claim 1
Note:	substitution is restricted
Note:	or pharmaceutically acceptable salts or solvates
Note:	or protected derivatives
Note:	also incorporates claim 38, formulas 11 and 12
Stereochemistry:	320-cis; 353-trans; 425-cis; 448-trans; 467-S; 477-S; 573-trans; 758-trans
Stereochemistry:	or stereoisomers

=> file reg

=>
Uploading C:\Program Files\Stnexp\Queries\28137453.str

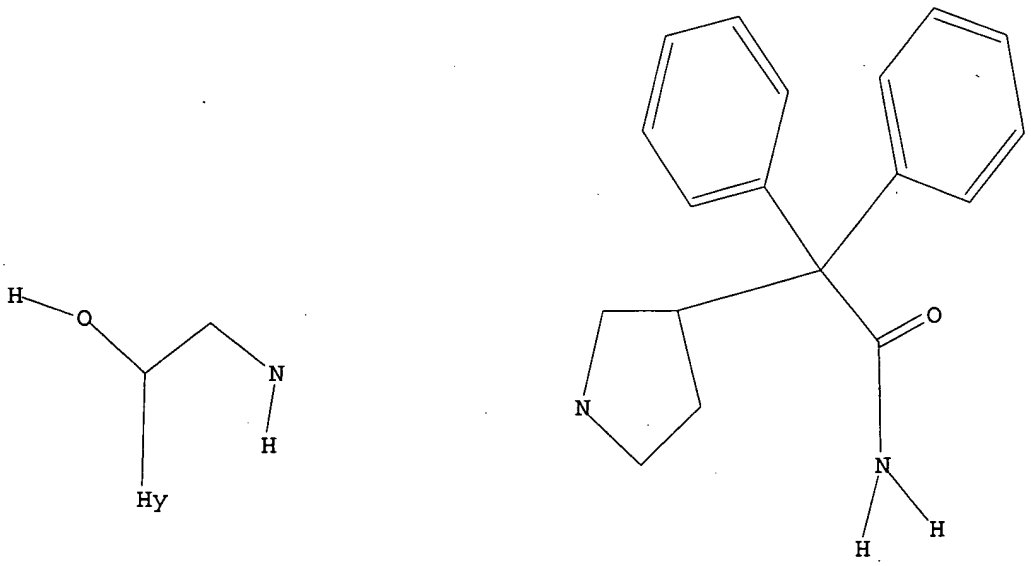


chain nodes :
1 2 3 4 5 6 12 15 16 17 18 19 30
ring nodes :
7 8 9 10 11 13 14 20 21 22 23 24 25 26 27 28 29
chain bonds :
1-4 1-2 1-30 2-3 3-6 4-5 10-12 12-13 12-14 12-15 15-16 15-17 17-18
17-19
ring bonds :
7-8 7-11 8-9 9-10 10-11 13-20 13-24 14-25 14-29 20-21 21-22 22-23 23-24
25-26 26-27 27-28 28-29
exact/norm bonds :
1-4 1-30 2-3 7-8 7-11 8-9 9-10 10-11 15-16 15-17
exact bonds :
1-2 3-6 4-5 10-12 12-13 12-14 12-15 17-18 17-19
normalized bonds :
13-20 13-24 14-25 14-29 20-21 21-22 22-23 23-24 25-26 26-27 27-28 28-29

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:CLASS 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom
27:Atom 28:Atom 29:Atom 30:Atom

L11 STRUCTURE UPLOADED

=> d l11
L11 HAS NO ANSWERS
L11 STR



Structure attributes must be viewed using STN Express query preparation.

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=> d his
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L13 0 L12 NOT L7

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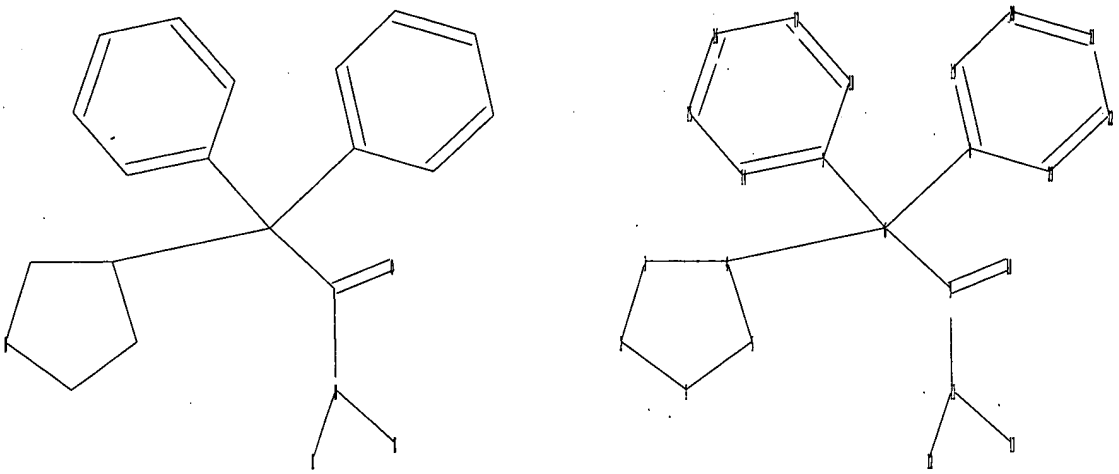

chain nodes :
6 9 10 11 12 13
ring nodes :
1 2 3 4 5 7 8 14 15 16 17 18 19 20 21 22 23
chain bonds :
4-6 6-7 6-8 6-9 9-10 9-11 11-12 11-13
ring bonds :
1-2 1-5 2-3 3-4 4-5 7-14 7-18 8-19 8-23 14-15 15-16 16-17 17-18 19-20
20-21 21-22 22-23
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 9-10 9-11
exact bonds :
4-6 6-7 6-8 6-9 11-12 11-13
normalized bonds :
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Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:Atom 8:Atom 9:CLASS 10:CLASS
11:CLASS 12:CLASS 13:CLASS 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom
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L14 STRUCTURE UPLOADED

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L14 HAS NO ANSWERS
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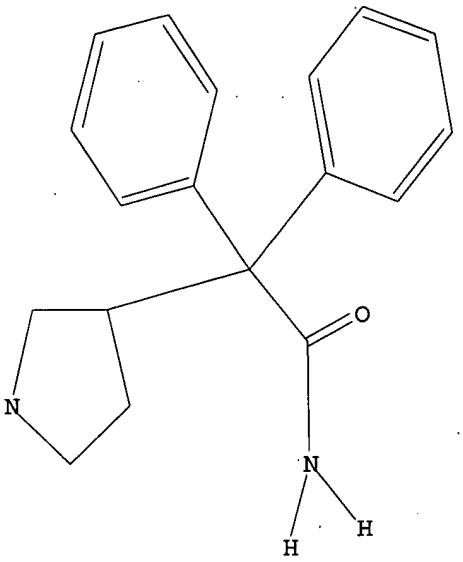

Structure attributes must be viewed using STN Express query preparation.

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=> s l15 not l7
L16          669 L15 NOT L7

=> file ca

=> s l16
L17          139 L16

=> s l17 not l8
L18          138 L17 NOT L8

=> s l18 and py<2004
      22713215 PY<2004
L19           73 L18 AND PY<2004

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L19  ANSWER 1 OF 73  CA  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        145:342445  CA
TITLE:                   Dual controlled release osmotic device comprising two
                         different active agents
INVENTOR(S):             Vergez, Juan A.; Ricci, Marcelo A.
PATENT ASSIGNEE(S):      Argent.
SOURCE:                  U.S. Pat. Appl. Publ., 29pp., Cont.-in-part of U.S.
                         Ser. No. 321,736.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  3
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006204578	A1	20060914	US 2006-355315	20060215
US 2003185882	A1	20031002	US 2001-992488	20011106 <--
US 2006177510	A1	20060810	US 2005-321736	20051229
PRIORITY APPLN. INFO.:			US 2001-992488	B3 20011106
			US 2005-321736	A2 20051229

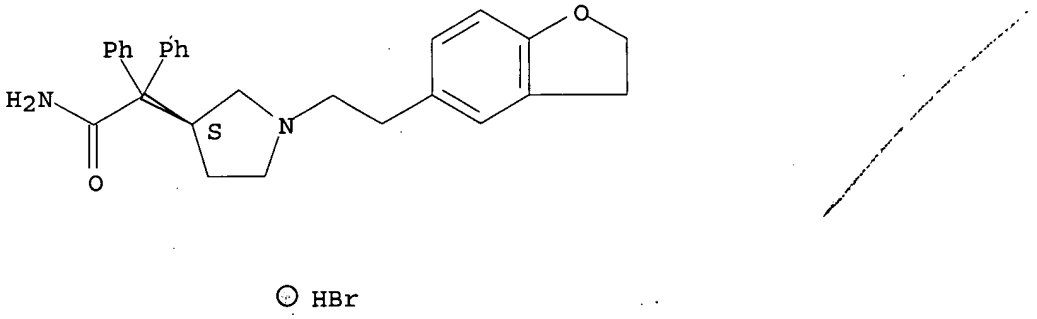
AB A dosage form that provides a controlled release of at least two different active agents is provided. Particular embodiments include a dosage form that provides therapeutically effective levels of a first active agent and a second active agent in a mammal for an extended period of time following oral administration. An osmotic device containing a bi-layered core is provided. The osmotic device provides a dual controlled release of both drugs from the core. The layers of the core are in stacked, substantially concentric or substantially eccentric arrangement. For example, bilayred controlled release tablet was prepared containing first layer comprised of oxybutynin hydrochloride 5.15 mg, Myvacet 5-07 10.80 mg, Povidone K25 5.40 mg, microcryst. cellulose spheres 68.68 mg, cellulose acetophtalate 4.10 mg, colloidal silicon dioxide 0.60 mg, and magnesium stearate 10.80 mg; second layer comprised of tolterodine L-tartrate 2.92 mg, Myvaplex 600P NF 82.07 mg, red iron oxide 0.15 mg, microcryst. cellulose spheres 67.76 mg, cellulose acetophtalate 4.10 mg, colloidal silicon dioxide 1.80 mg, croscarmellose sodium 1.80 mg, and magnesium stearate 0.75 mg.

IT 133099-07-7, Darifenacin Hydrobromide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dual controlled release osmotic device comprising two different active agents)

RN 133099-07-7 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, monohydrobromide, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



HBr

L19 ANSWER 2 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 140:349942 CA

TITLE: SVT-40776, a new selective M3 muscarinic antagonist: human receptor binding profile and bladder effects in the guinea pig

AUTHOR(S): Salcedo, C.; Balsa, D.; Enrich, A.; Davalillo, S.; Pellicer, T.; Lagunas, C.; Catena, J.; Fernandez-Serrat, A.; Farrerons, C.; Fernandez, A. G.

CORPORATE SOURCE: Laboratorios SALVAT, Spain

SOURCE: Neurourology and Urodynamics (2003), 22(5), 382-384
CODEN: NEUREM; ISSN: 0733-2467

PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

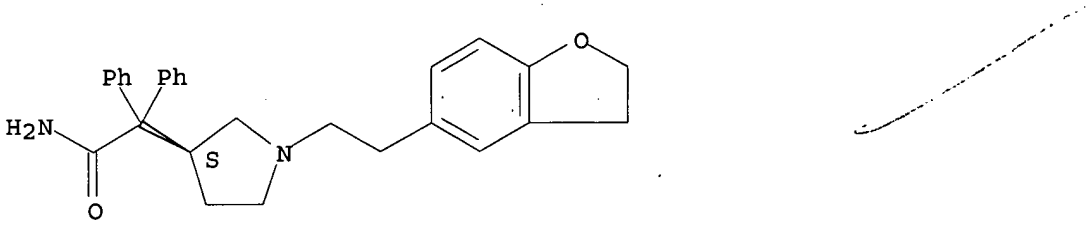
AB The study aims to determine the effect of SVT-40776, a novel substituted quinuclidine derivative with high M3 receptor affinity, on the different human muscarinic receptors through radioligand binding assays and to evaluate its activity on the intra-vesical and arterial pressure in anesthetized animals. SVT-40776 exhibits high affinity, in the sub-nanomolar range, for the human M3 muscarinic receptor, being the most potent ligand among all the reference compds. assayed. It also shows the highest selectivity of human M3 vs. the M2 subtype, among all the reference antagonists tested. SVT-40766 is the most potent compound inhibiting the bladder contractions, at the very low dose of 17.1 nmol/kg i.v.

IT 133099-04-4, Darifenacin
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison; human muscarinic receptor binding profile and effects on guinea pig bladder contraction of SVT-40776, a new selective M3 muscarinic antagonist)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 140:296791 CA

TITLE: Population pharmacokinetic modelling of darifenacin and its hydroxylated metabolite using pooled data, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability

AUTHOR(S): Kerbusch, Thomas; Waehlby, Ulrika; Milligan, Peter A.; Karlsson, Mats O.

CORPORATE SOURCE: Clinical Sciences, Department of Clinical Pharmacokinetics and Pharmacodynamics, Pfizer Global Research and Development, Kent, IPC 746, UK

SOURCE: British Journal of Clinical Pharmacology (2003), 56(6), 639-652
CODEN: BCPHBM; ISSN: 0306-5251

PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aims: A model describing the population pharmacokinetics of darifenacin and its hydroxylated metabolite was developed from a combined anal. of 18 studies. The relationships between explanatory covariates and pharmacokinetic parameters were explored. Methods: Plasma concentration data from 337 individuals were pooled from 17 Phase 1 studies (median 28/33

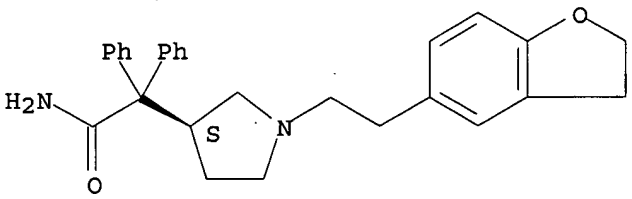
darifenacin/metabolite observations per healthy subject), and one Phase 2 study (median 7/7 darifenacin/metabolite observations per subject) encompassing one i.v. and five different oral formulations (1-45 mg). Results: Non-linear Mixed Effects Models (NONMEM Version VI) described both the population pharmacokinetics of darifenacin and its hydroxylated metabolite with a two-compartment disposition model with first order absorption. The values (mean ± standard error of the mean) for clearance (CL) and volume of distribution of the central compartment were 40.2±2.0 L h-1 and 34.7±4.6 L h-1, resp., in a typical male CYP2D6 homozygote-extensive metabolizer (Hom-EM). The absolute bioavailability (F) of darifenacin in a Hom-EM after doses of 7.5, 15 or 30 mg extended release formulation (CR) was 15, 19 and 25%, resp. Factors influencing F were formulation (70-110% higher for CR compared with immediate release following equivalent daily doses), CYP2D6 genotype [heterozygote-extensive metabolizers (Het-EM) and poor metabolizers (PM) experienced 40 and 90%, resp., higher exposure than Hom-EM irresp. of dose administered] and saturable first-pass metabolism (dose nonlinearity 1.05-1.43-fold). Race affected F, which was 56% lower in Japanese males. The CYP3A4 inhibitors ketoconazole and erythromycin increased F to approx. 100% and ketoconazole decreased CL by 67.5%. CL was 31% lower in females and 10% lower at night. Formulation affected the metabolite absorption/formation rate. Ketoconazole and erythromycin administration resulted in a decrease of 61.2 and 28.8% in exposure to the metabolite, resp. The covariates race, gender and circadian rhythm accounted for only approx. half of the variability in the estimated exposures to darifenacin. Conclusions: The pooled anal. provided a descriptive integration of all characteristics and covariates of the pharmacokinetics of darifenacin and its metabolite, enabling interpolation and extrapolation of these key factors.

IT 133099-04-4, UK 88525
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(population pharmacokinetic modeling of darifenacin and its hydroxylated metabolite, incorporating saturable first-pass metabolism, CYP2D6 genotype and formulation-dependent bioavailability)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:245956 CA
TITLE: Prediction of human pharmacokinetics from animal data and molecular structural parameters using multivariate regression analysis: Oral clearance
AUTHOR(S): Wajima, Toshihiro; Fukumura, Kazuya; Yano, Yoshitaka; Oguma, Takayoshi
CORPORATE SOURCE: Developmental Research Laboratories, Shionogi and

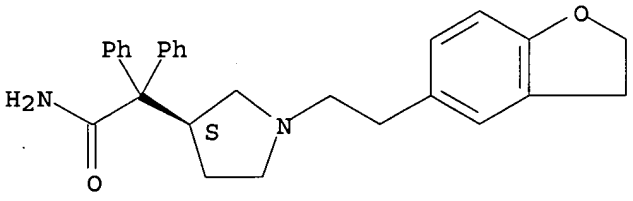
Company, Ltd., Osaka, 553-0002, Japan
SOURCE: Journal of Pharmaceutical Sciences (2003), 92(12), 2427-2440
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim of the study reported here was to develop a regression equation for predicting oral clearance of various kinds of drugs in humans using exptl. data from rats and dogs and mol. structural parameters. The data concerning the oral clearance of 87 drugs from rats, dogs, and humans were obtained from literature. The compds. have various structures, pharmacol. activities, and pharmacokinetic characteristics. In addition, the mol. weight, calculated partition coefficient (c log P), and the number of hydrogen bond acceptors were used as possible descriptors related to oral clearance in human. Multivariate regression analyses, multiple linear regression anal., and the partial least squares (PLS) method were used to predict oral clearance in human, and the predictive performances of these techniques were compared by allometric approaches, which have been used in interspecies scaling. Interaction terms were also introduced into the regression anal. to evaluate the nonlinear relationship. For the data set used in this study, the PLS model with the tertiary term descriptors gave the best predictive performance, and the value of the squared cross-validated correlation coefficient (q2) was 0.694. This PLS model, using animal oral clearance data for only two species and easily calculated mol. structural parameters, can generally predict oral clearance in human better than the allometric approaches. In addition, the mol. structural parameters and the interaction term descriptors were useful for predicting oral clearance in human by PLS. Another advantage of this PLS model is that it can be applied to drugs with various characteristics.

IT 133099-04-4, Darifenacin
RL: ANT (Analyte); PKT (Pharmacokinetics); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(prediction of human pharmacokinetics from animal data and mol. structural parameters using multivariate regression anal)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

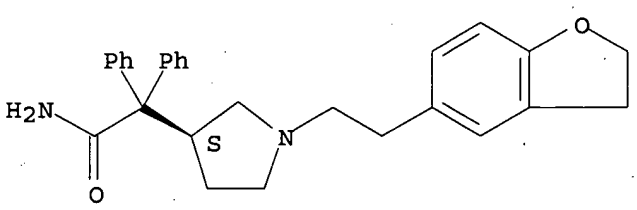


REFERENCE COUNT: 142 THERE ARE 142 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:210295 CA
TITLE: Pharmacological effects of darifenacin on human isolated urinary bladder
AUTHOR(S): Miyamae, Koichi; Yoshida, Masaki; Murakami, Shigetaka;

Iwashita, Hitoshi; Ohtani, Masayuki; Masunaga, Koichi; Ueda, Shoichi
CORPORATE SOURCE: Department of Urology, Kumamoto University School of Medicine, Kumamoto, Japan
SOURCE: Pharmacology (2003), 69(4), 205-211
CODEN: PHMGBN; ISSN: 0031-7012
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Darifenacin [(S)-2-2,2-diphenylacetamide] is a novel antimuscarinic drug currently undergoing phase III trials for the treatment of overactive bladder. We investigated the functional antagonist potency of darifenacin, and the antimuscarinic drugs propiverine, oxybutynin and atropine, on human detrusor smooth muscle. Urinary bladder specimens were obtained from 20 patients who underwent total cystectomy for malignant bladder tumor. Using an organ-bath technique, the effects of the compds. on carbachol-, KCl-, CaCl2- or elec. field stimulation (EFS)-induced contractions of the tissues were evaluated. The order of antagonist potency (pA2values) at the muscarinic M3 receptors was: darifenacin (9.34) > atropine (9.26) > oxybutynin (7.74) > propiverine (7.68). Darifenacin and atropine, at concns. up to 10-6 mol/l, did not inhibit the KCl- and CaCl2-induced contractions (concns. 80 and 5 mmol/l, resp.), while propiverine and oxybutynin (10-5 mol/l) significantly inhibited these contractions. Pretreatment with darifenacin (10-9-10-6 mol/l), propiverine (10-8- 10-5 mol/l), oxybutynin (10-8-10-5 mol/l) and atropine (10-9-10-6 mol/l) significantly inhibited maximum EFS-induced contractions. Darifenacin inhibited contractions of human detrusor smooth muscle only through its antimuscarinic action, while propiverine and oxybutynin had both antimuscarinic and Ca2+ channel antagonist actions. These findings indicate that darifenacin is a potent antagonist at the M3 receptor and support its use as a treatment for overactive bladder.
IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(pharmacol. effects of darifenacin on human isolated urinary bladder)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 73 CA
ACCESSION NUMBER: 140:157784 CA
TITLE: Existence of functional M3-muscarinic receptors in the human heart
AUTHOR(S): Willmy-Matthes, Pia; Leineweber, Kirsten; Wangemann, Thekla; Silber, Ralf-Edgar; Brodde, Otto-Erich
CORPORATE SOURCE: Institute of Pharmacology, University of Halle, Halle, 06097, Germany

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 368(4), 316-319
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

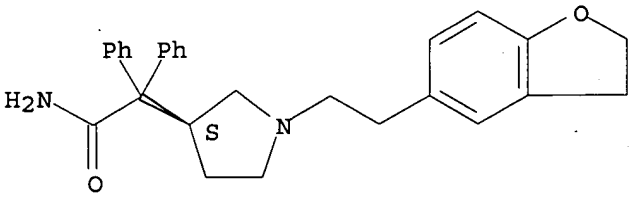
AB It has been recently shown that, in adult rat ventricular cardiomyocytes, functional muscarinic receptors (M-receptors) of the M3-subtype exist that mediate inositol phosphate (IP) formation. The aim of this study was to characterize the M-receptor subtype mediating IP formation in the human heart. For this purpose in [3H]-myo-inositol labeled slices of human right atria, carbachol-induced [3H]-IP formation and its inhibition by several M-receptor antagonists was assessed. Carbachol (0.1 μM-100 μM) increased [3H]-IP formation; maximal increase at 100 μM was 93±16% above basal (n=20); the pEC50-value for carbachol was 5.56. Atropine (1 μM) completely suppressed 100 μM carbachol-induced [3H]-IP formation. Among the M-receptor subtype "selective" antagonists himbacine (1 μM) and pirenzepine (1 μM) only marginally affected carbachol-induced [3H]-IP formation whereas the M3-receptor antagonist darifenacin (1 nM-1 μM) concentration-dependently inhibited carbachol-induced [3H]-IP formation with a pKi-value of 8.49. We conclude that in human right atrium there exist functional M3-receptors that couple to IP formation.

IT 133099-04-4, Darifenacin
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(effect on atrial IP formation; existence of functional M3-muscarinic receptors mediating inositol phosphate (IP) formation in human heart)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 73 CA

ACCESSION NUMBER: 140:139900 CA

TITLE: Muscarinic receptor subtypes in the human colon: lack of evidence for atypical subtypes

AUTHOR(S): Mansfield, Kylie J.; Mitchelson, Frederick J.; Moore, Kate H.; Burcher, Elizabeth
CORPORATE SOURCE: Department of Physiology and Pharmacology, University of New South Wales, Sydney, 2052, Australia

SOURCE: European Journal of Pharmacology (2003), 482(1-3), 101-109
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

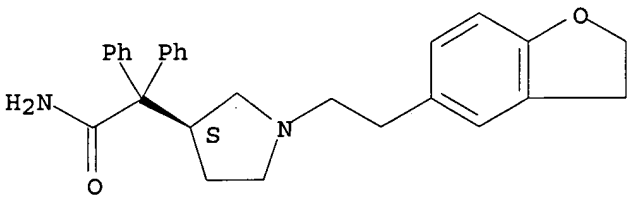
AB Characteristics of muscarinic receptors were investigated in circular muscle from normal human colon. In saturation studies (n=18), binding of [3H]quinuclidinyl benzylate (QNB) was of high affinity (Kd 87.3 pM) and capacity (Bmax 362±27 fmol/mg protein), with no differences between ascending and sigmoid colon. Kinetic studies gave a Kd of 55 pM. Methoctramine and darifenacin displayed biphasic binding profiles, the high affinity components being compatible with a population of approx. 80±5% M2 and 13±2% M3 muscarinic receptors, resp. Pirenzepine, mamba toxin 1 and mamba toxin 3 were very weak competitors, indicating negligible expression of muscarinic M1 and M4 receptors. Six other subtype-preferring antagonists exhibited Ki values typical of those reported at cloned human muscarinic M2 receptors. In the presence of methoctramine, pre-treatment with alkylating agent 4-diphenylacetoxy-N-(2-chloroethyl)-piperidine hydrochloride (4-DAMP mustard) inhibited [3H]quinuclidinyl benzylate binding to 26% of sites. Following alkylation of muscarinic M3 receptors, darifenacin bound to a single low affinity site, indicating binding to muscarinic M2 receptors.

IT 133099-04-4, Darifenacin
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(muscarinic receptor subtype characterization by various ligands in human colon in relation to lack of evidence for atypical subtypes)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 8 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 140:59523 CA

TITLE: Preparation of phenylalkylamines and pyridylalkylamines as 5-HT1A serotonergic ligands.

INVENTOR(S): Leonardi, Amedeo; Motta, Gianni; Riva, Carlo; Guarneri, Luciano

PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003106421	A2	20031224	WO 2003-EP6290	20030616 <--
WO 2003106421	A3	20040617		

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IT 2002MI1329	A1	20031215	IT 2002-MI1329		20020614 <--
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PRIORITY APPLN. INFO.:			IT 2002-MI1329	A	20020614
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			WO 2003-EP6290	W	20030616

OTHER SOURCE(S): MARPAT 140:59523
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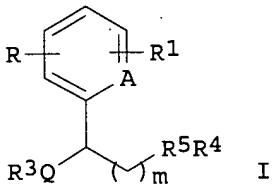

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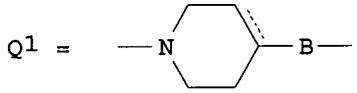


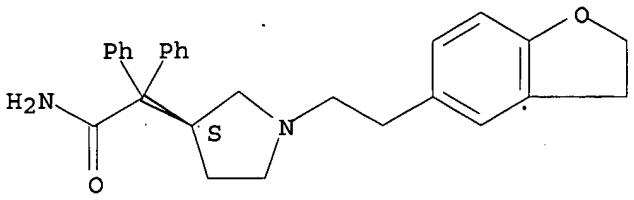
AB Title compds. [I; R = H, halo, alkyl, alkoxy, alkylthio, OH, halo, alkenyl, alkynyl, alkylcarbonyl, alkylsulfinyl, alkylsulfonyl, dialkylaminosulfonyl, etc.; R1 = H, (substituted) cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heterocycloalkyl, heterocycycloxy, heterocycloalkoxy; Q = CO, CH(OH), CH(OR2); R2 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl; R3 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl; R4 = (substituted) aryl, heterocyclyl; A = CH, N; R5 = NR6(CH2)nR7, Q1; m, n = 2, 3; R6 = H, alkyl; R7 = O, S, NR6, CH2; B = bond, O, S, NR6, CH2; dotted line = optional double bond; with provisos], were prepared for treatment of neuromuscular dysfunction of the lower urinary tract (no data). Thus, 3-(2-cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde (preparation given), 8-(N-methyl-2-aminoethoxy)quinoline, and Na(AcO)3BH were stirred with AcOH in CH2Cl2 for 1 h to give 52% 8-[N-[3-(2-cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy]quinoline.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of phenylalkylamines and pyridylalkylamines as 5-HT1A serotonergic ligands)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

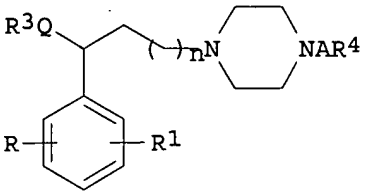


L19 ANSWER 9 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:42211 CA
TITLE: Preparation of phenylalkylpiperazines for treatment of diseases related to 5-HT1A receptor activity.
INVENTOR(S): Leonardi, Amadeo; Motta, Gianni; Riva, Carlo; Poggesi, Elena
PATENT ASSIGNEE(S): Recordati S.A., Switz.; Recordati Industria Chimica e Farmaceutica S.p.A.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003106443	A1	20031224	WO 2003-EP6289	20030616 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IT 2002MI1327	A1	20031215	IT 2002-MI1327	20020614 <--
CA 2489449	A1	20031224	CA 2003-2489449	20030616 <--
AU 2003246434	A1	20031231	AU 2003-246434	20030616 <--
US 2004072839	A1	20040415	US 2003-463196	20030616
BR 2003011804	A	20050329	BR 2003-11804	20030616
EP 1549627	A1	20050706	EP 2003-759960	20030616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1659155	A	20050824	CN 2003-813675	20030616
JP 2006502102	T	20060119	JP 2004-513275	20030616
NZ 537470	A	20060630	NZ 2003-537470	20030616
NO 2005000147	A	20050314	NO 2005-147	20050111

PRIORITY APPLN. INFO.:	IT 2002-MI1327	A	20020614
	US 2002-505350P	P	20020614
	WO 2003-EP6289	W	20030616

OTHER SOURCE(S): MARPAT 140:42211
GI



I

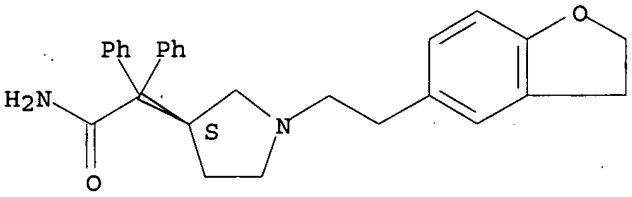
AB Title compds. [I; R = H, halo, alkyl, alkoxy, alkylthio, OH, alkenyl, alkynyl, haloalkyl, aminoalkyl, cyano, alkylsulfonyl, dialkylaminosulfonyl, etc.; R1 = H, (R-substituted) cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heterocyclyloxy, heterocycloalkyl, heterocycloalkoxy; Q = CO, CH(OH), CH(OR2); R2 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl; R3 = H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl; R4 = (R-substituted) aryl, heterocyclyl; n = 1, 2; A = bond, CH2, CH2CH2], were prepared for treatment of CNS disorders, for reducing the frequency of bladder contractions, and for treating neuromuscular dysfunction of the lower urinary tract. Thus, 4-cyclohexyl-3-(2-fluorophenyl)-4-methoxybutyraldehyde (preparation given), 1-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine hydrochloride, Na triacetoxyborohydride, AcOH and CH2Cl2 were stirred together at room temperature for 1h, and kept overnight to give 1-[4-cyclohexyl-3-(2-fluorophenyl)-4-methoxybutyl]-4-[2-(2,2,2-trifluoroethoxy)phenyl]piperazine. The latter bound to 5-HT1A receptors with Ki = 1.45 nM.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of phenylalkylpiperazines for treatment of diseases related to 5-HT1A receptor activity)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 10 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 139:391384 CA

TITLE: Use of inhibitors of EGFR-mediated signal transduction for the treatment of benign prostatic hyperplasia (BPH)/prostatic hypertrophy

INVENTOR(S): Singer, Thomas; Colbatzky, Florian; Platz, Stefan

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany

SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 2003094921	A2	20031120	WO 2003-EP4606		20030502	<--
WO 2003094921	A3	20040318				
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW						
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG						
DE 10221018	A1	20031127	DE 2002-10221018		20020511	<--
AU 2003233223	A1	20031111	AU 2003-233223		20030502	<--
CA 2483590	A1	20031120	CA 2003-2483590		20030502	<--
EP 1505981	A2	20050216	EP 2003-727422		20030502	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK						
JP 2005526123	T	20050902	JP 2004-503006		20030502	
US 2003225079	A1	20031204	US 2003-431699		20030508	<--
PRIORITY APPLN. INFO.:			DE 2002-10221018	A	20020511	
			US 2002-389815P	P	20020618	
			WO 2003-EP4606	W	20030502	

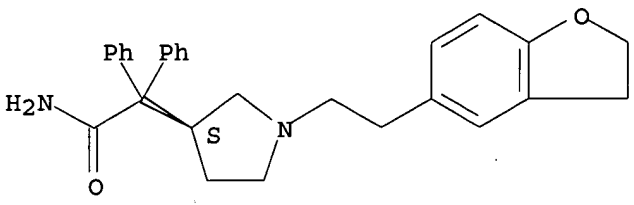
OTHER SOURCE(S): MARPAT 139:391384

AB The invention discloses the use of EGF-receptor antagonists for the production of a medicament to prevent and/or treat benign prostatic hyperplasia and/or prostatic hypertrophy, as well as a method for the treatment or prevention of benign prostatic hyperplasia/prostatic hypertrophy involving the administration of an EGF-receptor antagonist, optionally in combination with known compds. for the treatment of benign prostatic hyperplasia/prostatic hypertrophy, and the corresponding pharmaceutical compns. Compds. of the invention include e.g. quinazoline derivs. and monoclonal antibodies. Preparation of 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(N-(2-methoxyethyl)-N-methylamino)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline is described.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(EGFR-mediated signal transduction inhibitors for treatment of benign prostatic hyperplasia/prostatic hypertrophy)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

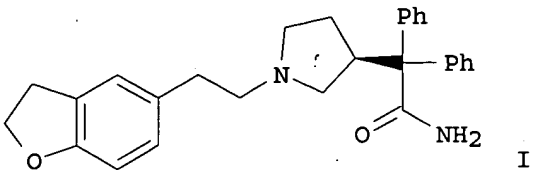


L19 ANSWER 11 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:292143 CA
TITLE: Preparation of stable hydrate of a muscarinic receptor antagonist, (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide hydrate
INVENTOR(S): Dunn, Peter James; Matthews, John George; Newbury, Trevor Jack; O'Connor, Garry
PATENT ASSIGNEE(S): Novartis International Pharmaceutical Ltd., Bermuda
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080599	A1	20031002	WO 2003-IB1043	20030317 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2480287	A1	20031002	CA 2003-2480287	20030317 <--
AU 2003209921	A1	20031008	AU 2003-209921	20030317 <--
EP 1490357	A1	20041229	EP 2003-744716	20030317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008706	A	20050104	BR 2003-8706	20030317
CN 1642945	A	20050720	CN 2003-807084	20030317
JP 2005524678	T	20050818	JP 2003-578353	20030317
US 2003191176	A1	20031009	US 2003-396887	20030325 <--
US 6930188	B2	20050816		
US 2005245597	A1	20051103	US 2005-180433	20050713

PRIORITY APPLN. INFO.:		
GB 2002-7104	A	20020326
US 2002-374893P	P	20020423
WO 2003-IB1043	W	20030317
US 2003-396887	A3	20030325

GI



I

AB Disclosed is stable solid hydrate of a muscarinic receptor antagonist, i.e. (S)-2-[1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl]-2,2-diphenylacetamide (I) hydrate. I.H2O is suitable for topical transdermal or buccal administration and useful in the treatment of irritable bowel syndrome, diverticular disease, esophageal achalasia, chronic obstructive airways disease, over active bladder (including symptoms of incontinence, urge and frequency), urinary incontinence, neurogenic urinary urgency or pollakiuria, treatment of bladder functional disorder, urinary leakage, painful or difficult urination caused by neurogenic bladder, spastic or hypertonic bladder, dysfunctional bladder syndrome, gastrointestinal disorders including gastrointestinal hyperactivity, and relaxing effect on intestinal smooth muscle cells. Thus, a solution of I toluene solvate (16 g, 0.031 mol) in MeCN (320 mL) was concentrated under reduced pressure at ambient temperature The resulting foam was dissolved in MeCN (48 mL) to which was added water (1:1.1 mL) dropwise at ambient temperature The solution was stirred at ambient temperature until crystallization occurs and was allowed to stir overnight. I.H2O was collected by filtration and dried under vacuum at ambient temperature (10.4 g, 76% yield). I.H2O was further converted into I.HBr by treatment with 48% aqueous HBr solution in 2-butanone.

IT 608127-90-8P
RL: IMF (Industrial manufacture); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(powder X-ray diffraction data; preparation of stable [[(dihydrobenzofuranyl)ethyl]pyrrolidinyl]diphenylacetamide hydrate as muscarinic receptor antagonist for treatment of bladder and gastrointestinal disorders)

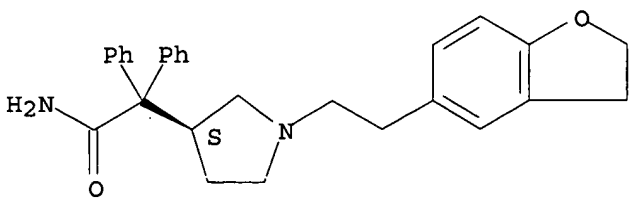
RN 608127-90-8 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)-, compd. with methylbenzene (1:1) (9CI) (CA INDEX NAME)

CM 1

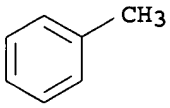
CRN 133099-04-4
CMF C28 H30 N2 O2

Absolute stereochemistry.



CM 2

CRN 108-88-3
CMF C7 H8



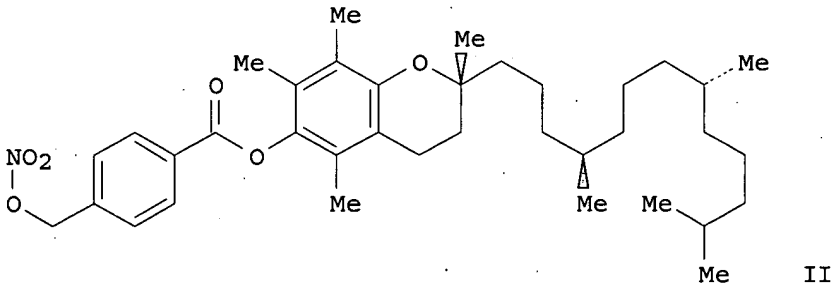
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 12 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:214237 CA
TITLE: Preparation of nitrate prodrugs able to release nitric oxide in a controlled and selective way and their use for prevention and treatment of inflammatory, ischemic and proliferative diseases
INVENTOR(S): Scaramuzzino, Giovanni
PATENT ASSIGNEE(S): Italy
SOURCE: Eur. Pat. Appl., 313 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1336602	A1	20030820	EP 2002-425075	20020213 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: EP 2002-425075 20020213
GI



II

AB New pharmaceutical compds. of general formula F-(X)q (I) [q = 1-5, preferably 1; F is chosen among drugs such as δ-tocopherol, clidanac, diethylhomospermine, glucosamine, thymocartin, vofopitant, etc.; X is chosen among 4 groups M, T, V, and Y where M = ONO2, nitrate salt, nitrite ester, ONO, thoinitrite, SNO, etc., T = OR1-M, OR1OR1-M, SR1NR2R1-M, NR2R1-M, NR2R1SR1-M, etc., R1 = saturated or unsatd., linear or branched alkylene, having 1 to 21 carbon atoms or a saturated or unsatd., optionally heterosubstituted or branched cycloalkylene, having 3 to 7 carbon atoms or an optionally heterosubstituted arylene having 3 to 7

carbon atoms; R2 = H, saturated or unsatd., linear or branched 1-21 carbon atom alkyl, saturated or unsatd. optionally heterosubstituted or branched 3-7 carbon cycloalkyl, optionally heterosubstituted 3-7 carbon aryl; R1, R2 = OH, SH, F, Cl, Br, OPO3H2, CO2H, etc.; bond between F and T = carboxylic ester, carboxylic amide, glycoside, azo, thioester, sulfonic ester, etc.; V = Z-M2, OZ-M2, NR2Z-M2, R1Z-M2, OR1-M2, OR1Z-M2, M2 = M, R1-M, OR1-M, SR1-M, NR2R1-M; ZM2 = COCH2CH(M2)CH2N+Me3, COCH2CH2COM2, COCH(NHR2)CH2M2, etc.; Y = 4-COC6H4CH2ONO2, O(CH2)4ONO2, COCH(NH2)CH2ONO2, 3-OC6H4CH2ONO2, etc.] were prepared For example, α-tocopherol reacted with 4-HO2CC6H4CH2ONO2 to give the nitroxymethyl derivative II. The compds. of general formula I are nitrate prodrugs which can release nitric oxide in vivo in a controlled and selective way and without hypotensive side effects and for this reason they are useful for the preparation of medicines for prevention and treatment of inflammatory, ischemic, degenerative and proliferative diseases of musculoskeletal, tegumental, respiratory, gastrointestinal, genito-urinary and central nervous systems.

IT 586349-92-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nitrate prodrugs for treating or preventing inflammatory, ischemic, degenerative, and proliferative diseases)

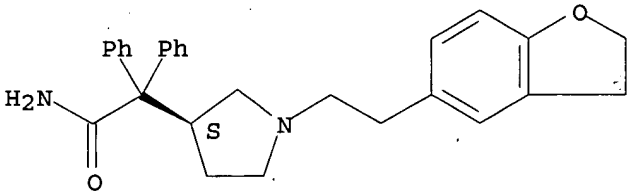
RN 586349-92-0 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)-, mononitrate (9CI) (CA INDEX NAME)

CM 1

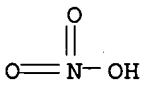
CRN 133099-04-4
CMF C28 H30 N2 O2

Absolute stereochemistry.



CM 2

CRN 7697-37-2
CMF H N O3



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 13 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:207821 CA
TITLE: Use of cyclooxygenase inhibitors and antimuscarinic agents for the treatment of incontinence

INVENTOR(S): Versi, Ebrahim
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070233	A1	20030828	WO 2003-US4561	20030214 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2475374	A1	20030828	CA 2003-2475374	20030214 <--
AU 2003211078	A1	20030909	AU 2003-211078	20030214 <--
EP 1476146	A1	20041117	EP 2003-742765	20030214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003007772	A	20041207	BR 2003-7772	20030214
CN 1633283	A	20050629	CN 2003-804160	20030214
JP 2005526040	T	20050902	JP 2003-569190	20030214
US 2003191172	A1	20031009	US 2003-368091	20030218 <--
PRIORITY APPLN. INFO.:			US 2002-357888P P	20020219
			WO 2003-US4561 W	20030214

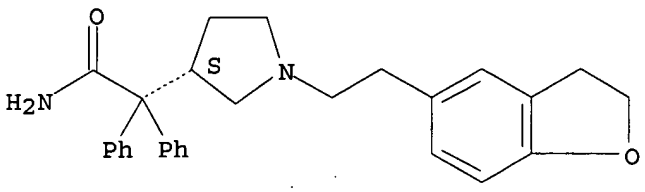
AB The invention provides a method for the use of a cyclooxygenase-2 inhibitor, alone or in combination with an antimuscarinic agent, for the treatment or prophylaxis of a urinary incontinence condition in a subject in need of such treatment or prevention, comprising administering to the subject an effective amount of the cyclooxygenase-2 inhibitor and, optionally, the antimuscarinic agent.

IT 586346-94-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase inhibitors and antimuscarinic agents for treatment of incontinence)

RN 586346-94-3 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, monohydrochloride, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 14 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:90459 CA
TITLE: Use of an immediate-release powder in pharmaceutical and nutraceutical compositions
INVENTOR(S): Besse, Jerome; Besse, Laurence
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003124191	A1	20030703	US 2002-106923	20020325 <--
FR 2834212	A1	20030704	FR 2001-16934	20011227 <--
FR 2834212	B1	20040709		
CA 2471903	A1	20030710	CA 2002-2471903	20021227 <--
WO 2003055464	A1	20030710	WO 2002-FR4575	20021227 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2002364489	A1	20030715	AU 2002-364489	20021227 <--
EP 1458356	A1	20040922	EP 2002-799854	20021227
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BR 2002015380	A	20041207	BR 2002-15380	20021227
US 2005118272	A1	20050602	US 2003-500213	20021227
JP 2005520799	T	20050714	JP 2003-556042	20021227
HU 200500509	A2	20050928	HU 2005-509	20021227
NO 2004003172	A	20040914	NO 2004-3172	20040726
PRIORITY APPLN. INFO.:			FR 2001-16934 A	20011227
			WO 2002-FR4575 W	20021227

AB The present invention relates to the use of a powder comprising at least one active substance, at least one surfactant, at least one wetting agent

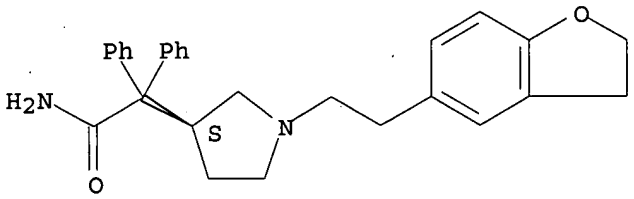
and at least one diluent, for preparing a pharmaceutical or nutraceutical composition, this composition allowing rapid and immediate release of the active substance. Granules containing phloroglucinol 10, sorbitol 89, and propylene glycol 1% were prepared

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of immediate-release powder in pharmaceutical and nutraceutical compns.)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 15 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 139:57943 CA

TITLE: Darifenacin for the treatment of overactive bladder

INVENTOR(S): Colli, Enrico; Quinn, Paul; Serdarevic, Dzelal; Skillern, Laurence Howard

PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.

SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051354	A1	20030626	WO 2002-IB664	20020305 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2469702	A1	20030626	CA 2002-2469702	20020305 <--
AU 2002236141	A1	20030630	AU 2002-236141	20020305 <--
EP 1458376	A1	20040922	EP 2002-702623	20020305
EP 1458376	B1	20061004		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002014925	A	20041221	BR 2002-14925	20020305
CN 1604777	A	20050406	CN 2002-824936	20020305
HU 200402625	A2	20050428	HU 2004-2625	20020305

JP 2005516925	T	20050609	JP 2003-552287		20020305
AT 341323	T	20061015	AT 2002-702623		20020305
US 2003130338	A1	20030710	US 2002-256420		20020926 <--
ZA 2004004289	A	20050812	ZA 2004-4289		20040601
NO 2004002586	A	20040618	NO 2004-2586		20040618
PRIORITY APPLN. INFO.:			GB 2001-29962	A	20011214
			US 2002-347456P	P	20020111
			WO 2002-IB664	W	20020305

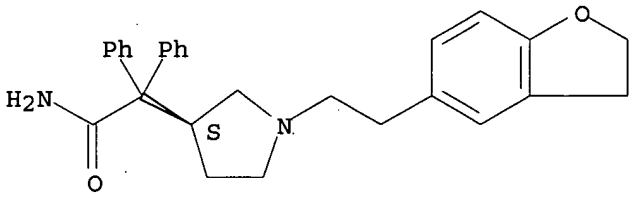
AB The invention provides the use of darifenacin, or a derivative in the manufacture of a drug for the reduction of urgency in patients suffering from overactive bladder. Thus, slow-release tablets containing darifenacin were administered to the patients suffering from overactive bladder. The drug produced a dose-related reduction in the urgency and severity of the urgency.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(darifenacin for treatment of overactive bladder)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 16 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	139:30677 CA
TITLE:	Functional Role of Central Muscarinic Receptors for Micturition in Normal Conscious Rats
AUTHOR(S):	Ishizuka, Osamu; Gu, Bao Jun; Yang, Zhang Xiao; Nishizawa, Osamu; Andersson, Karl-Erik
CORPORATE SOURCE:	Dep. Urol., Shinshu Univ. Sch. Med., Matsumoto, Japan
SOURCE:	Journal of Urology (Hagerstown, MD, United States) (2002), 168(5), 2258-2262 CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB PURPOSE: Antimuscarinic agents, which are used in to treat urgency and urge incontinence, have well-known effects on peripheral muscarinic receptors. However, some currently used drugs may have effects on muscarinic receptors in the brain and/or spinal cord involved in voiding control. The authors tested if muscarinic receptors within the central nervous system mediate a tonic excitatory influence on voiding in rats and if these receptors can be differently influenced by antimuscarinic drugs. MATERIALS AND METHODS: The effects on cystometrog. of intracerebroventricular atropine, oxybutynin, tolterodine and darifenacin were investigated in normal conscious rats. RESULTS: Atropine (0.2 to 2 nmol.) dose dependently affected urodynamic parameters. At 2 nmol. in 6

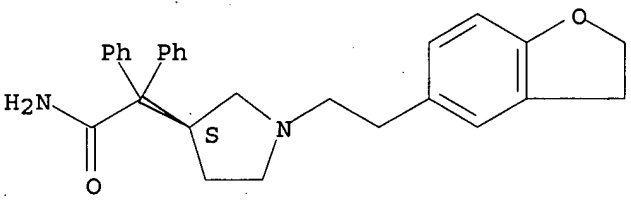
rats the drug decreased voiding pressure (p <0.01), and increased bladder capacity (p <0.001), voided volume (p <0.05) and post-void residual volume (p <0.05). In 6 rats oxybutynin (6 to 40 nmol.) given at a dose of 6 nmol. caused no change in cystometric parameters, while at 20 nmol. the drug decreased voiding pressure (p <0.01). Tolterodine (2 to 20 nmol.) dose dependently changed urodynamic parameters, while at 20 nmol. in 6 rats the drug decreased voiding pressure (p <0.01) and increased bladder capacity (p <0.05) and voided volume (p <0.05). Darifenacin given at a dose of 20 nmol. in 6 rats caused no change in cystometric parameters. CONCLUSIONS: Muscarinic receptor mechanisms in the central nervous system mediate a tonic excitatory influence on voiding in rats, while nonsubtype selective antimuscarinic drugs may have an inhibitory effect on these mechanisms.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(functional role of central muscarinic receptors for micturition in normal conscious rats)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 17 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:26684 CA
TITLE: Method of treating irritable bowel syndrome
INVENTOR(S): Dunn, Peter James; Humphrey, Michael John; Quinn, Paul
PATENT ASSIGNEE(S): Pfizer Inc., UK
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003114356	A1	20030619	US 2002-218735	20020813 <--
US 6653339	B2	20031125		

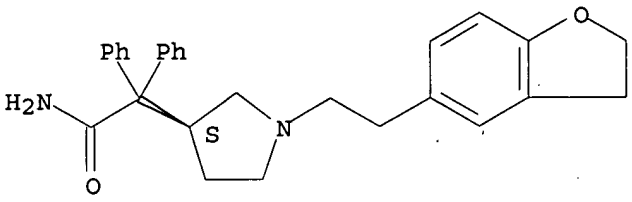
PRIORITY APPLN. INFO.: GB 2001-19919 A 20010815
US 2001-315554P P 20010828

AB The present invention is directed to a method for the treatment of irritable bowel syndrome comprising the multiple daily pulse dosing of an immediate release formulation of the anti-muscarinic darifenacin. Dosing two or three times a day is particularly preferred.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiple daily pulse dosing of darifenacin for treating irritable

bowel syndrome)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 18 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:406917 CA
TITLE: Buccal sprays or capsules containing drugs for treating disorders of the gastrointestinal or urinary tracts
INVENTOR(S): Dugger, Harry A., III
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U.S. Ser. No. 537,118.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 19
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003095926	A1	20030522	US 2002-230085	20020829 <--
WO 9916417	A1	19990408	WO 1997-US17899	19971001 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 1029536	A1	20000823	EP 2000-109347	19971001 <--
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EP 1036561	A1	20000920	EP 2000-109357	19971001 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2497112	A1	20040311	CA 2003-2497112	20030827
WO 2004019910	A2	20040311	WO 2003-US26854	20030827
WO 2004019910	A3	20040729		
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AU 2003272242		A1	20040319	AU 2003-272242	20030827
EP 1534242		A2	20050601	EP 2003-754415	20030827
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JP 2006506342		T	20060223	JP 2004-531570	20030827
US 2004136914		A1	20040715	US 2003-671717	20030929
US 2004136915		A1	20040715	US 2003-671719	20030929
US 2005025716		A1	20050203	US 2004-928996	20040827
US 2006198790		A1	20060907	US 2006-429953	20060509
PRIORITY APPLN. INFO.:				WO 1997-US17899	A2 19971001
				US 2000-537118	A2 20000329
				EP 1997-911621	A3 19971001
				US 2002-230085	A 20020829
				WO 2003-US26854	W 20030827
				US 2003-671717	A3 20030929

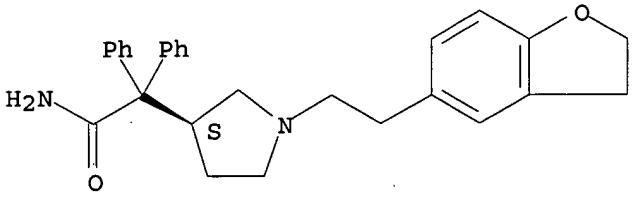
AB Buccal aerosol sprays or capsules using polar and non-polar solvent have now been developed which provide biol. active compds. for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal polar compns. of the invention comprise formulation I: aqueous polar solvent, active compound, and optional flavoring agent; formulation II: aqueous polar solvent, active compound, optionally flavoring agent, and propellant; formulation III: non-polar solvent, active compound, and optional flavoring agent; and formulation IV: non-polar solvent, active compound, optional flavoring agent, and propellant. A lingual spray contained famotidine 7-20, water 5-10, L-aspartic acid 5-10, polyethylene glycol 50-85, and flavors 2-5%.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buccal sprays or capsules containing drugs for treating disorders of gastrointestinal or urinary tracts)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 19 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	138:358515 CA
TITLE:	Pharmaceutical compositions containing oxybutynin
INVENTOR(S):	Vergez, Juan A.; Ricci, Marcelo A.
PATENT ASSIGNEE(S):	Osmotica Costa Rica Sociedad Anonima, Costa Rica
SOURCE:	PCT Int. Appl., 90 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	Spanish
FAMILY ACC. NUM. COUNT:	3
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039436	A2	20030515	WO 2002-CR7	20021106 <--
WO 2003039436	A3	20040226		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003185882	A1	20031002	US 2001-992488	20011106 <--
AU 2002363361	A1	20030519	AU 2002-363361	20021106 <--
PRIORITY APPLN. INFO.:			US 2001-992488 A	20011106
			WO 2002-CR7 W	20021106

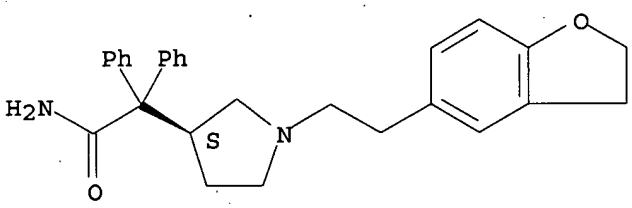
AB The invention relates to a pharmaceutical composition and a dosage form for treating incontinence with oxybutynin and a second drug. The aforementioned drug substance can be any drug that is used to treat incontinence. The dosage form can include, independently, therapeutic or subtherapeutic quantities of oxybutynin and the second drug, depending on the administration method, the dosage form employed and the second drug used. Particular configurations of said composition include a dosage form that releases oxybutynin and the second drug in a controlled manner in order to maintain effective therapeutic levels of oxybutynin and/or the second drug in a mammal for an extended period of time. According to the invention, an osmotic device is provided which comprises a double-layer core. The aforementioned osmotic device provides dual controlled release of both drugs from the core. The invention also relates to a method of treating urinary incontinence (stress or emergency) with a pharmaceutical composition and a dosage form. The combination of the oxybutynin and the second drug provides an improved general clin. benefit in relation to all other agents which are administered alone, with approx. the same dose.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing oxybutynin)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 20 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 138:276286 CA

TITLE: Pharmaceutical compositions containing muscarinic antagonists and 5α-reductase inhibitors for urinary tract disorder treatment

INVENTOR(S): Arneric, Stephen P.; Andersson, Per-Olof
PATENT ASSIGNEE(S): Pharmacia AB, Swed.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003026564	A2	20030403	WO 2002-SE1748	20020926 <--
WO 2003026564	A3	20031211		
WO 2003026564	A9	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003060513	A1	20030327	US 2001-965556	20010927 <--
CA 2461731	A1	20030403	CA 2002-2461731	20020926 <--
EP 1438035	A2	20040721	EP 2002-775633	20020926
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BR 2002012824	A	20041013	BR 2002-12824	20020926
JP 2005503424	T	20050203	JP 2003-530203	20020926

PRIORITY APPLN. INFO.:
US 2001-965556 A 20010927
SE 2001-3858 A 20011120
WO 2002-SE1748 W 20020926

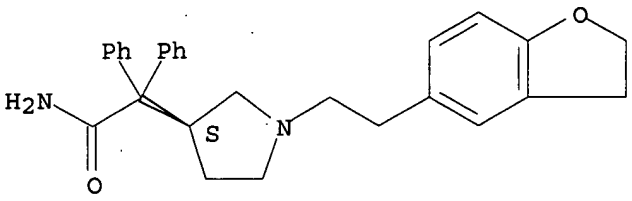
AB The present invention concerns the field of urol. The invention provides a pharmaceutical composition comprising a combination of a first compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, and precursors and salts, and a second compound selected from the group consisting of 5-HT1a receptor agonists and antagonists, and precursors and salts thereof, and optionally a carrier or a diluent. There is also provided a method of treatment of urinary disorders in a mammal, including humans. A pharmaceutical composition is prepared by combining tolterodine with a neutral 5-HT1a receptor antagonist in a carrier. The composition contains 0.05-4 mg tolterodine/kg patient body weight (e.g., 3-240 mg tolterodine for a person weighing 60 kg) and 0.01-1 mg of neutral 5-HT1a receptor antagonist/kg of patient body weight The composition is administered to a patient for the treatment of incontinence, and particularly stress incontinence, urge incontinence or mixed incontinence.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing muscarinic antagonists and 5α-reductase inhibitors for urinary tract disorder treatment)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 21 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:260465 CA
TITLE: Pharmaceutical composition comprising receptor agonists and antagonists treatment of urinary disorder
INVENTOR(S): Arneric, Stephen P.; Andersson, Per-Olof
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003060513	A1	20030327	US 2001-965556	20010927 <--
CA 2461731	A1	20030403	CA 2002-2461731	20020926 <--
WO 2003026564	A2	20030403	WO 2002-SE1748	20020926 <--
WO 2003026564	A3	20031211		
WO 2003026564	A9	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1438035	A2	20040721	EP 2002-775633	20020926
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002012824	A	20041013	BR 2002-12824	20020926
CN 1558756	A	20041229	CN 2002-818876	20020926
JP 2005503424	T	20050203	JP 2003-530203	20020926
US 2004116533	A1	20040617	US 2003-729764	20031205
ZA 2004002362	A	20050120	ZA 2004-2362	20040325

PRIORITY APPLN. INFO.:			
	US 2001-965556	A	20010927
	SE 2001-3858	A	20011120
	WO 2002-SE1748	W	20020926

AB The present invention concerns the field of urol. The invention provides a novel pharmaceutical composition, comprising a pharmaceutically effective combination of (i) a first compound selected from the group consisting of muscarinic receptor antagonists, 5α-reductase inhibitors, and α-adrenergic receptor antagonists, and precursors and pharmaceutically acceptable salts thereof, and (ii) a second compound selected from the group consisting of 5-HT1a receptor agonists and

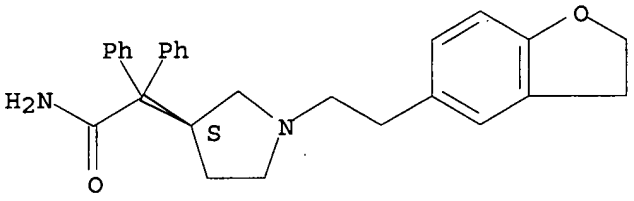
antagonists, and precursors and pharmaceutically acceptable salts thereof, and optionally a pharmaceutically acceptable carrier or diluent therefor. There is also provided a method of therapeutical treatment of urinary disorder in a mammal, including man, comprising administering to said mammal, including man, in need of such treatment, a therapeutically effective amount of a composition according to the invention. A pharmaceutical composition contained between about 2 mg to about 20 mg of 5a-reductase inhibitor and between about 0.5 mg to about 50 mg of neutral 5-HT1a receptor antagonist. The composition is administered to a patient for the treatment of urinary disorder.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical composition comprising receptor agonists and antagonists treatment of urinary disorder)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 22 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 138:248554 CA

TITLE: Combination of selected opioids with muscarinic antagonists for treating urinary incontinence and increased urinary urgency

INVENTOR(S): Christoph, Thomas

PATENT ASSIGNEE(S): Gruenenthal G.m.b.H., Germany

SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024444	A1	20030327	WO 2002-EP10460	20020918 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10146275	A1	20030424	DE 2001-10146275	20010918 <--
CA 2460655	A1	20030327	CA 2002-2460655	20020918 <--

EP 1429754	A1	20040623	EP 2002-779368		20020918
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002012714	A	20040803	BR 2002-12714		20020918
HU 200401485	A2	20041129	HU 2004-1485		20020918
JP 2005507387	T	20050317	JP 2003-528540		20020918
NZ 531777	A	20061130	NZ 2002-531777		20020918
NO 2004001059	A	20040512	NO 2004-1059		20040312
US 2004242617	A1	20041202	US 2004-803187		20040318
ZA 2004002853	A	20041217	ZA 2004-2853		20040415
PRIORITY APPLN. INFO.:			DE 2001-10146275	A	20010918
			WO 2002-EP10460	W	20020918

OTHER SOURCE(S): MARPAT 138:248554

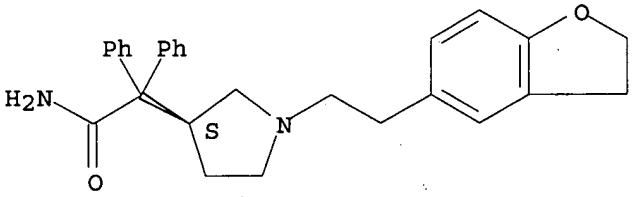
AB The invention discloses the use of a combination of opioids and antimuscarinic drugs, and other predominantly peripherally active substances, for producing a medicament used for treating increased urinary urgency or urinary incontinence. The invention also discloses corresponding medicaments and methods for treating increased urinary urgency or urinary incontinence.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid-muscarinic antagonist combination for treating urinary incontinence and increased urinary urgency)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 23 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 138:193282 CA

TITLE: Use of α-adrenoceptor antagonist in combination with muscarinic antagonist for medicament

INVENTOR(S): Wayley, Michael Grant

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: Jpn. Kokai Tokkyo Koho, 36 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003055261	A	20030226	JP 2001-240717	20010808 <--
PRIORITY APPLN. INFO.:			JP 2001-240717	20010808

AB The invention relates to pharmaceutical combinations suitable for treating

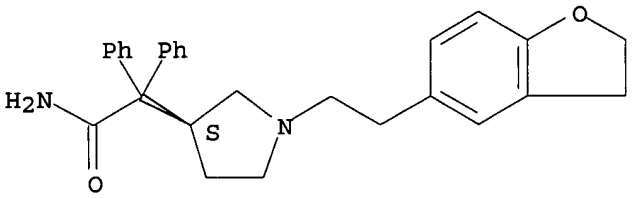
the lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in men, which combinations contain an α-adrenoceptor antagonist and a muscarinic antagonist. The combinations of the invention are particularly suitable for treating moderate or severe LUTS. A combination immediate-release darifenacin/doxazosin tablet containing doxazosin mesylate 4.05, darifenacin hydrobromide 2.976, microcryst. cellulose 125.28, lactose 63.694, sodium starch glycollate 2, magnesium stearate 2 mg was prepared

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of α-adrenoceptor antagonist in combination with muscarinic antagonist for treatment of benign prostatic hyperplasia)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 24 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 138:100837 CA

TITLE: Muscarinic receptors in isolated urinary bladder smooth muscle from different mouse strains

AUTHOR(S): Choppin, A.

CORPORATE SOURCE: Genitourinary-Pharmacology, Deltagen, Inc., Menlo Park, CA, 94025, USA

SOURCE: British Journal of Pharmacology (2002), 137(4), 522-528
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 1 The pharmacol. characteristics of muscarinic receptors in male and female mouse urinary bladder smooth muscle from different strains (C57Bl/6, 129/SvJ and hybrid backcross N1F2) were studied. 2 (+)-Cis-dioxolane, oxotremorine-M, acetylcholine, carbachol and pilocarpine induced concentration-dependent contractions of the urinary bladder smooth muscle (range for pEC50 = 6.4-6.6, 6.2-6.7, 6.2-6.4, 5.4-6.0 and 0.0-5.1, Tmax=1.9-4.7 g, 1.3-3.4 g, 1.0-3.0 g, 1.4-2.4 and 0.0-0.3 g, resp., n=4-6 depending on the gender and the strain). In females, these contractions were competitively antagonized by a range of muscarinic receptor antagonists (pKB value range, depending on the strain): atropine (8.0-8.9), pirenzepine (6.1-6.4), 4-DAMP (7.6-8.4), methoctramine (5.6-6.1), p-F-HHSiD (7.5-7.7), zamifenacin (7.7-8.4) and darifenacin (8.2-8.7). 3 In recontraction studies, in which the muscarinic M3 receptor population was decreased, and conditions optimized to study M2 receptor activation, methoctramine exhibited an affinity estimate consistent with muscarinic M3 receptors (pKB=6.26±0.08, pA2=6.31±0.07; pKB=6.09±0.22, pA2=6.08±0.01 for female inbred strain 129/SvJ and hybrid backcross N1F2, resp.) or intermediate between the one expected for this compound at M2 and M3 receptors, (pKB=6.66±0.08, pA2=7.00±0.27

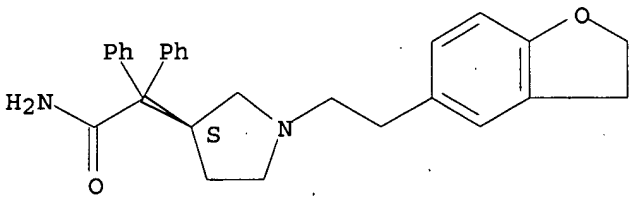
for female inbred strain C57BL/6). 4 These data study suggest that muscarinic M3 receptors are the predominant, if not the exclusive, subtype mediating contractile responses to muscarinic agonists in female mouse urinary bladder smooth muscle, with strain differences.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); BIOL (Biological study)
(pharmacol. characteristics of muscarinic receptors in isolated urinary bladder smooth muscle from different mouse strains)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 25 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 138:78464 CA

TITLE: Pharmaceutical preparations based on active ingredients susceptible to illicit administration

INVENTOR(S): Garavani, Alberto; Marchiorri, Maurizio; Di Martino, Alessandro

PATENT ASSIGNEE(S): Altergon S.A., Switz.

SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

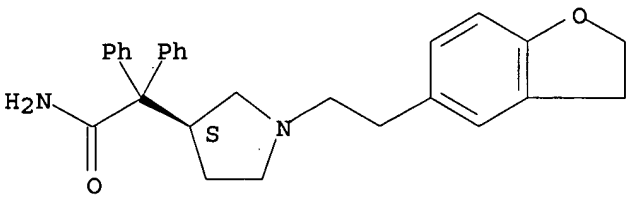
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1273301	A2	20030108	EP 2002-15073	20020705 <--
EP 1273301	A3	20030409		
EP 1273301	B1	20060906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
AT 338567	T	20060915	AT 2002-15073	20020705

PRIORITY APPLN. INFO.: IT 2001-MI1446 A 20010706

AB Disclosed are pharmaceutical formulations for oral administration, preferably in the form of a soft capsule enclosing an active principle susceptible to illicit administration and at least one pharmaceutically acceptable organoleptic marker which is particularly evident for its odor, taste or color or for its scarce miscibility with food. The active principle is selected from the group consisting of a substance acting on the central nervous system and/or as a narcotic and of a substance with anabolizing activity or the like. The organoleptic marker is independently selected out of one or more substances belonging to the group consisting of flavoring agents, flavoring agents, coloring agents, odorants, and oils.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical prepns. based on active ingredients susceptible to illicit administration containing organoleptic markers)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

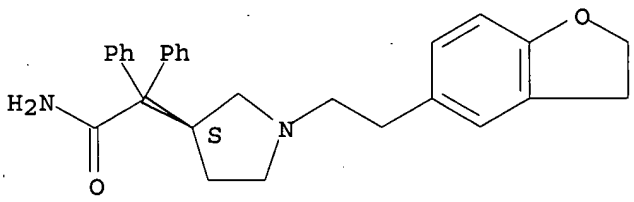
Absolute stereochemistry.



L19 ANSWER 26 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:66945 CA
TITLE: The subtypes of muscarinic receptors for neurogenic bladder contraction in rats
AUTHOR(S): Hirose, Hiroyasu; Aoki, Ikuo; Kimura, Toshifumi; Fujikawa, Toru; Numazawa, Tomoshige; Sasaki, Kaori; Nishikibe, Masaru; Noguchi, Kazuhito
CORPORATE SOURCE: Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Ibaraki, Tsukuba, 300-2611, Japan
SOURCE: European Journal of Pharmacology (2002), 452(2), 245-253
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors evaluated in vivo functional selectivity profiles for muscarinic M2 and M3 subtypes of four muscarinic antagonists: Compound A (a novel muscarinic receptor antagonist with M2-sparing antagonistic activity), darifenacin, (a muscarinic M3 receptor antagonist); methoctramine (a muscarinic M2 receptor antagonist) and tolterodine (a nonselective muscarinic receptor antagonist), and compared the inhibition potency on distention-induced bladder contraction in rats. In an in vivo functional study, Compound A (0.03-10 mg/kg, i.v.) showed antimuscarinic activity with high selectivity for M3 (salivation) over M2 (bradycardia) (>100-fold). Darifenacin (0.01-0.3 mg/kg, i.v.) showed only slight selectivity for M3 over M2 (3.7-fold). Methoctramine (0.003-1 mg/kg, i.v.) showed the reverse selectivity profile (0.077-fold). Tolterodine (0.003-0.3 mg/kg, i.v.) showed less selectivity (1.2-fold). Compound A at M3 inhibitory doses (0.1 and 0.3 mg/kg, i.v.) showed inhibition in a distention-induced neurogenic bladder contraction model, and its maximal inhibitory effects were about 60% at an even higher dose (3 mg/kg). Methoctramine at M2 inhibitory doses (0.03 and 0.1 mg/kg, i.v.) did not significantly affect distention-induced bladder contraction. When tolterodine and darifenacin caused inhibition of distention-induced bladder contraction, its maximal inhibitory effects were similar to that of Compound A. Therefore, these findings suggest that Compound A would be an excellent pharmacol. tool to give a better understanding of which subtypes of muscarinic receptors act in bladder function so far, and muscarinic M3, but not M2, receptors mainly mediate the cholinergic component of distention-induced bladder contraction.

IT 133099-04-4, Darifenacin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(muscarinic receptors subtypes for neurogenic bladder contraction in rat)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 27 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:237773 CA
TITLE: Combined diffusion/osmotic pumping drug delivery system
INVENTOR(S): Faour, Joaquina
PATENT ASSIGNEE(S): Osmotica Corp., Argent.
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. 6,352,721.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002132005	A1	20020919	US 2002-47915	20020115 <--
US 6753011	B2	20040622		
US 6352721	B1	20020305	US 2000-483282	20000114 <--
WO 2001051035	A1	20010719	WO 2001-US562	20010108 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-483282 A2 20000114
WO 2001-US562 A 20010108

AB Delivery devices capable of delivering one or more active substances by diffusion through plural micropores in the membrane or by osmotic pumping through one or more preformed passageways in the membrane are provided. The device has an about centrally located expandable core completely surrounded by an active substance-containing layer, which is completely surrounded by the membrane. The device is capable of delivering insol.,

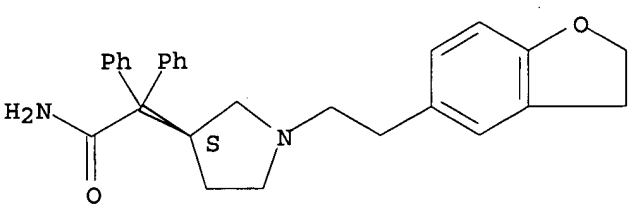
slightly soluble, sparingly soluble and very soluble active substances to an environment of use. The preferred delivery rate is zero order. The device can deliver an active substance for a period of about 12-24 h. Formulation of a coated tablets containing nifedipine is disclosed. The amount of nifedipine release from the tablet after 24 h was 94.8%.

IT 133099-04-4, Darifenacin.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined diffusion/osmotic pumping drug delivery system)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 28 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:163810 CA
TITLE: Topical smooth muscle tone modulators for the treatment of esophageal motility disorders and gastroesophageal reflux disease
INVENTOR(S): Kamm, Michael Albert
PATENT ASSIGNEE(S): UK
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062324	A2	20020815	WO 2002-GB310	20020124 <--
WO 2002062324	A3	20021114		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2437380	A1	20020815	CA 2002-2437380	20020124 <--
EP 1357905	A2	20031105	EP 2002-716161	20020124 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1491106	A	20040421	CN 2002-804542	20020124
BR 2002006980	A	20040706	BR 2002-6980	20020124
JP 2004521898	T	20040722	JP 2002-562331	20020124

US 2004063684	A1	20040401	US 2003-467154		20031022
PRIORITY APPLN. INFO.:			GB 2001-2854	A	20010205
			GB 2001-2855	A	20010205
			GB 2001-2856	A	20010205
			WO 2002-GB310	W	20020124

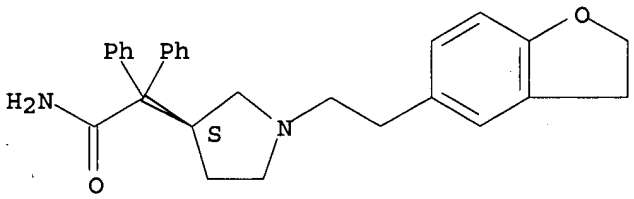
AB Smooth muscle tone modulators are applied topically to treat esophageal motility disorders and gastroesophageal reflux disease. Topical application of the smooth muscle tone modulators reduces the risk of the unwanted side effects observed from oral or sublingual administration of the modulators.

IT 133099-04-4, Darifenacin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical smooth muscle tone modulators for treatment of esophageal motility disorders and gastroesophageal reflux disease)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 29 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	137:163148 CA
TITLE:	Irritable bowel syndrome neuropharmacology: A review of approved and investigational compounds
AUTHOR(S):	Callahan, Michael J.
CORPORATE SOURCE:	Department of Medical Affairs, Novartis Pharmaceuticals Inc., East Hanover, NJ, 07936, USA
SOURCE:	Journal of Clinical Gastroenterology (2002), 35(1, Suppl.), S58-S67 CODEN: JCGADC; ISSN: 0192-0790
PUBLISHER:	Lippincott Williams & Wilkins
DOCUMENT TYPE:	Journal; General Review
LANGUAGE:	English

AB A review. Anticholinergics and prokinetics are mainstays of therapy for Irritable Bowel Syndrome (IBS) patients despite their limited efficacy and troublesome side-effect profile. The clin. limitations of these drugs are a result of their relative broad and nonspecific pharmacol. interaction with various receptors. Recent advances in gut physiol. have led to the identification of various receptor targets that may play a pivotal role in the pathogenesis of IBS. Medicinal chemists searching for safe and effective IBS therapies are now developing compds. targeting many of these specific receptors. The latest generation of anticholinergics, such as zamifenacin, darifenacin, and YM-905, provide selective antagonism of the muscarinic type-3 receptor. Tegaserod, a selective 5-HT4 partial agonist, tested in multiple clin. trials, is effective in reducing the symptoms of abdominal pain, bloating, and constipation. Ezlopitant and nepadudant, selective antagonists for neurokinin receptors type 1 and type 2, resp., show promise in reducing gut motility and pain. Loperamide, a mu (μ) opioid receptor agonist, is safe and effective for IBS patients with

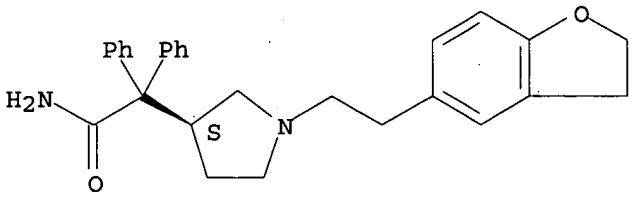
diarrhea (IBS-D) as the predominant bowel syndrome. Fedotozine, a kappa (κ) opioid receptor agonist, has been tried as a visceral analgesic in various clin. trials with conflicting results. Alosetron, a 5-HT3 receptor antagonist, has demonstrated efficacy in IBS-D patients but incidents of ischemic colitis seen in post-marketing follow-up resulted its removal from the market. Compds. that target cholecystokinin A, N-methyl-D-aspartate, alpha2-adrenergic, and corticotropin-releasing factor receptors are also examined in this review.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irritable bowel syndrome neuropharmacol.: approved and investigational compds.)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

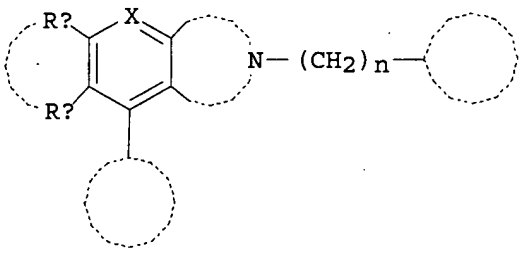


REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 30 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:83636 CA
TITLE: Combination drugs containing NK-1 receptor antagonists and NK-2 receptor antagonists and/or cholinolytics
INVENTOR(S): Doi, Takayuki; Hashimoto, Tadatoshi; Kamo, Izumi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002051440	A1	20020704	WO 2001-JP11231	20011221 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2432543	A1	20020704	CA 2001-2432543	20011221 <--
JP 2002249432	A	20020906	JP 2001-390486	20011221 <--
EP 1352659	A1	20031015	EP 2001-271853	20011221 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
US 2004058914 A1 20040325 US 2003-451431 20030623
PRIORITY APPLN. INFO.: JP 2000-391013 A 20001222
WO 2001-JP11231 W 20011221
OTHER SOURCE(S): MARPAT 137:83636
GI



I

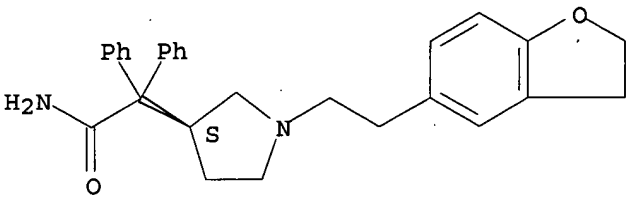
AB Disclosed are drugs useful as preventives and remedies for urinary frequency, urinary incontinence, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, arthritis deformans, pain, cough, irritable bowel syndrome, vomiting, depression, anxiety, manic-depression or schizophrenia which comprise a combination of an NK-1 receptor antagonist and an NK-2 receptor antagonist and/or a cholinolytic. More specifically, drugs comprising a combination of a compound represented by the following formula I [wherein the ring M represents a heterocycle having, as the partial structure -X-Y< thereof, -N=C<, -CO-N< or -CS-N<; Ra and Rb are bonded to each other to form the ring A, or Ra and Rb may be the same or different and each represents hydrogen or a substituent in the ring M; the rings A and B are each an optionally substituted homocycle or heterocycle and at least one of them is an optionally substituted heterocycle; the ring C is an optionally substituted homocycle or heterocycle; the ring Z is an optionally substituted nitrogen-containing heterocycle; and n is an integer of 1 to 6], its salt or a prodrug thereof with an NK-2 receptor antagonist and/or a cholinolytic. The effect of (9R)-7-[3,5-bis(trifluoromethyl)benzyl]-6,7,8,9,10,11-hexahydro-9-methyl-5-(4-methylphenyl)-6,13-dioxo-13H-[1,4]diazocino[2,1-g][1,7] naphthyridine and (±)SR48968 (saredutant) hydrochloride in cyclophosphamide-induced urinary frequency rats were examined

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination drugs containing NK-1 receptor antagonists and NK-2 receptor antagonists and/or cholinolytics)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

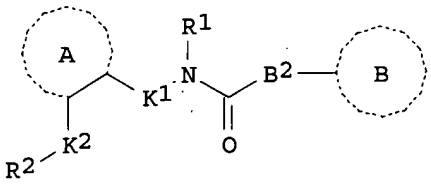
L19 ANSWER 31 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:325431 CA
TITLE: Preparation of 2-biphenyl 4-piperidinyl ureas having muscarinic receptor antagonist activity
INVENTOR(S): Mammen, Mathai; Oare, David
PATENT ASSIGNEE(S): Theravance, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 69 pp., Cont.-in-part of U. S. Ser. No.456,170, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 31
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 2002049195	A1	20020425	US 2000-732514	20001207	<--
US 6635764	B2	20031021			
US 6693202	B1	20040217	US 2000-645609	20000825	
EP 1457488	A1	20040915	EP 2004-12859	20001207	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
ES 2225275	T3	20050316	ES 2000-982493	20001207	
ES 2243333	T3	20051201	ES 2000-983991	20001207	
ZA 2002004553	A	20030908	ZA 2002-4553	20020606	<--
ZA 2002004557	A	20030908	ZA 2002-4557	20020606	<--
US 2004110229	A1	20040610	US 2003-425368	20030429	
US 2004054187	A1	20040318	US 2003-426364	20030430	
US 2004116706	A1	20040617	US 2003-426270	20030430	

PRIORITY APPLN. INFO.:

US 1999-456170	B2	19991207
US 1999-120287P	P	19990216
US 1999-325725	B2	19990604
US 2000-645609	A1	20000825
EP 2000-982493	A3	20001207
US 2000-732514	A1	20001207

OTHER SOURCE(S): MARPAT 136:325431
GI



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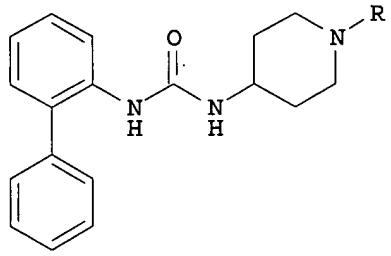


II

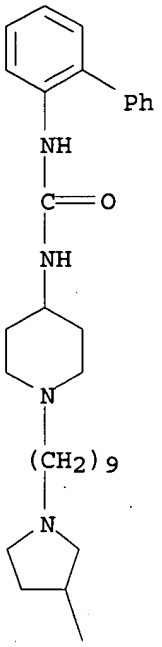
AB The title compds. L1XL2 [L1 = I (wherein A = (hetero)aryl; B2 = NRa; Ra = H, alkyl, etc.; R1 = H, alkyl; R2 = heteroaryl, etc.; K1 = a bond, alkylene; K2 = a bond, CO, SOn, etc.; n = 0-2; B = heterocycloamino, heteroarylamino); X = a linker; L2 = an organic group comprising at least one primary, secondary, or tertiary amine] which are muscarinic receptor antagonists and agonists (biol. data given), were prepared and formulated. E.g., a 2-step preparation of the intermediate II [R = H] starting with biphenyl-2-isocyanate and 4-amino-N-benzylpiperidine, was given. Mass spec data for 643 compds. II [R = XL2] such as II [X = CH2CH(OH)CH2; L2 = 4-[2-(N-phenyl-N-methylamino)-2-oxoethyl]piperazin-1-yl], were presented.

IT 344433-58-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2-biphenyl 4-piperidinyl ureas having muscarinic receptor antagonist activity)

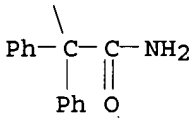
RN 344433-58-5 CA

CN 3-Pyrrolidineacetamide, 1-[9-[4-[[([1,1'-biphenyl]-2-ylamino)carbonyl]amino]-1-piperidinyl]nonyl]-α,α-diphenyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L19 ANSWER 32 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:178015 CA
TITLE: Drugs for incontinence - salified and nonsalified nitric oxide-donors and phosphodiesterase inhibitors
INVENTOR(S): Del Soldato, Piero; Benedini, Francesca
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011707	A2	20020214	WO 2001-EP8734	20010727 <--
WO 2002011707	A3	20021205		

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IT 2000MI1848	A1	20020208	IT 2000-MI1848	20000808 <--
IT 1318674	B1	20030827		
AU 200191691	A	20020218	AU 2001-91691	20010727 <--
EP 1307184	A2	20030507	EP 2001-971798	20010727 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004511436	T	20040415	JP 2002-517044	20010727
US 2003203899	A1	20031030	US 2003-343330	20030206 <--
PRIORITY APPLN. INFO.:			IT 2000-MI1848 A	20000808
			WO 2001-EP8734 W	20010727

OTHER SOURCE(S): MARPAT 136:178015

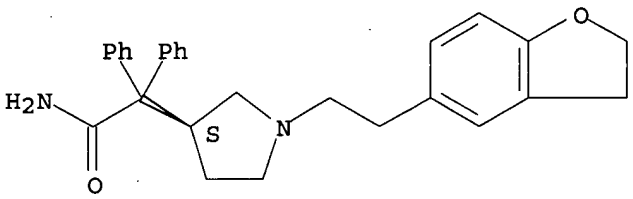
AB Use in the incontinence of one or more of the following classes of drugs selected from the following: (B) salified and nonsalified nitric oxide-donor drugs, of formula: A - X1 - N(O)z, (B') nitrate salts of drugs used for the incontinence, and which do not contain in the mol. a nitric oxide donor group; (C) organic or inorg. salts of compds. inhibiting phosphodiesterases.

IT 133099-04-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(salified and nonsalified nitric oxide-donors and phosphodiesterase inhibitors for treatment of incontinence)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 33 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 136:938 CA

TITLE: Pharmacological characterization of muscarinic receptors in mouse isolated urinary bladder smooth muscle

AUTHOR(S): Choppin, A.; Eglen, R. M.

CORPORATE SOURCE: Genitourinary-Pharmacology, Neurobiology Unit, Roche Bioscience, Palo Alto, CA, 94304, USA

SOURCE: British Journal of Pharmacology (2001), 133(7), 1035-1040
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacol. characteristics of muscarinic receptors in the male mice urinary bladder smooth muscle were studied. (+)-Cis-dioxolane, oxotremorine-M, acetylcholine, carbachol and pilocarpine induced concentration-dependent contractions of the urinary bladder smooth muscle (pEC50=6.6±0.1, 6.9±0.1, 6.7±0.1, 5.8±0.1 and 5.8±0.1,

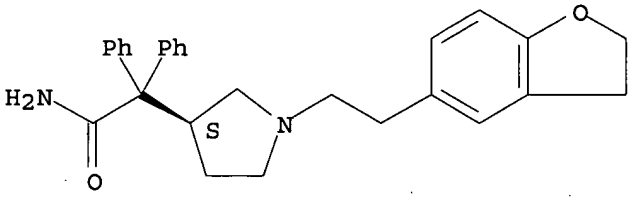
EMax=3.2±0.8 g, 2.7±0.4 g, 1.0±0.1 g, 2.7±0.3 and 0.9±0.2 g, resp., n=4). These contractions were competitively antagonized by a range of muscarinic receptor antagonists (pKB values): atropine (9.22±0.09), pirenzepine (6.85±0.08), 4-DAMP (8.42±0.14), methoctramine (5.96±0.05), p-F-HHSiD (7.48±0.09), tolterodine (8.89±0.13), AQ-RA 741 (7.04±0.12), s-secoverine (8.21±0.09), zamifenacin (8.30±0.17) and darifenacin (8.70±0.09). In this tissue, the pKB values correlated most favorably with pKi values for these compds. at human recombinant muscarinic M3 receptors. A significant correlation was also noted at human recombinant muscarinic m5 receptors given the poor discriminative ability of ligands between M3 and m5 receptors. In recontraction studies, in which the muscarinic M3 receptor population was decreased, and conditions optimized to study M2 receptor activation, methoctramine exhibited an affinity estimate consistent with muscarinic M3 receptors (pKB=6.23±0.14; pA2=6.16±0.03). Overall, these data study suggest that muscarinic M3 receptors are the predominant, if not the exclusive, subtype mediating contractile responses to muscarinic agonists in male mouse urinary bladder smooth muscle.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacol. characterization of muscarinic receptors in mouse isolated urinary bladder smooth muscle)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 34 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 135:313448 CA

TITLE: Effects of YM905, a novel muscarinic M3-receptor antagonist, on experimental models of bowel dysfunction in vivo

AUTHOR(S): Kobayashi, Seiji; Ikeda, Ken; Suzuki, Mami; Yamada, Toshimitsu; Miyata, Keiji

CORPORATE SOURCE: Pharmacology Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, 305-8585, Japan

SOURCE: Japanese Journal of Pharmacology (2001), 86(3), 281-288
CODEN: JJPAAZ; ISSN: 0021-5198

PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the effects of YM905 [(+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate], a

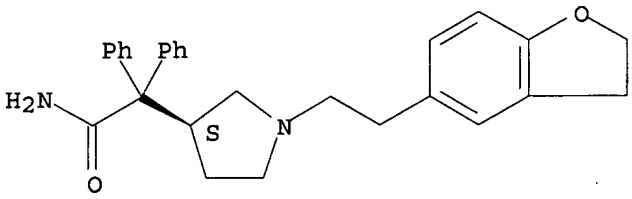
new orally active muscarinic M3-receptor antagonist, on bowel dysfunction in vivo using exptl. models that reproduce the symptoms present in irritable bowel syndrome (IBS). YM905 potently inhibited restraint stress-induced fecal pellet output in fed rats (ED50: 4.0 mg/kg) and diarrhea in fasted rats (ED50: 1.7 mg/kg), with similar potencies to the inhibition of bethanechol-, neostigmine- and nicotine-induced fecal pellet output in rats (ED50: 3.3, 7.9 and 4.5 mg/kg, resp.). YM905 also inhibited 5-hydroxytryptamine (5-HT)-, prostaglandin E2- and castor oil-induced secretory diarrhea in mice (ED50: 5.5, 14 and 6.3 mg/kg, resp.), but showed no significant effect on cholera toxin-induced intestinal secretion in mice. In addition, YM905 (3, 10 mg/kg) reversed morphine-decreased postprandial defecation in ferrets, a model of spastic constipation, whereas ramosetron, a 5-HT3-receptor antagonist, was not effective. The mode of YM905 action was similar to that of darifenacin, a selective M3-receptor antagonist, with equivalent potencies. By contrast, propantheline, an antimuscarinic drug that has been used for IBS, was much less potent. These results show that YM905 ameliorates a wide spectrum of bowel dysfunctions through the blockade of M3 receptors, suggesting its therapeutic potential for treating IBS.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of YM905 on exptl. models of bowel dysfunction)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 35 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:200472 CA
TITLE: Norepinephrine reuptake inhibitor and antimuscarinic agent combinations
INVENTOR(S): Rogosky, Karen; Jorn, Deborah
PATENT ASSIGNEE(S): Pharmacia & Upjohn Co., USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062236	A2	20010830	WO 2001-US3698	20010123 <--
WO 2001062236	A3	20020307		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1257277	A2	20021120	EP 2001-910421		20010123 <--
EP 1257277	B1	20050615			
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JP 2003523382	T	20030805	JP 2001-561303		20010123 <--
NZ 520975	A	20040326	NZ 2001-520975		20010123
CN 1660435	A	20050831	CN 2005-10003943		20010123
PT 1257277	T	20050930	PT 2001-910421		20010123
CA 2399442	A1	20010830	CA 2001-2399442		20010223 <--
AU 2001038028	A5	20010903	AU 2001-38028		20010223 <--
AU 781254	B2	20050512			
US 2002010216	A1	20020124	US 2001-792718		20010223 <--
AT 297735	T	20050715	AT 2001-910421		20010223
ES 2241802	T3	20051101	ES 2001-1910421		20010223
PRIORITY APPLN. INFO.:			US 2000-184790P	P	20000224
			CN 2001-804031	A3	20010123
			WO 2001-US3698	W	20010123

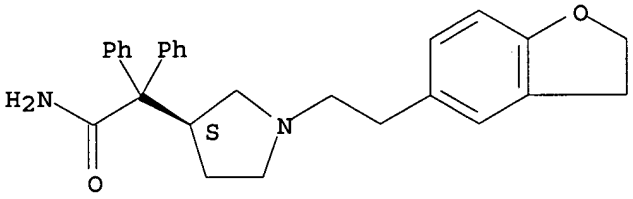
AB A composition comprising: (a) a pharmaceutically effective amount of one or more norepinephrine reuptake inhibitors or a pharmaceutically effective salt thereof; and (b) a pharmaceutically effective amount of one or more antimuscarinic agents or a pharmaceutically effective salt thereof is provided. The composition is useful in treating disorders or diseases of the central nervous system, and particularly useful in treating incontinence. A composition was prepared containing reboxetine in either its racemic of (S,S) enantiomer forms with tolterodine.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(norepinephrine reuptake inhibitor and antimuscarinic agent combinations)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 36 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	135:185453 CA
TITLE:	Pharmaceutical combinations for treating lower urinary tract disfunctions
INVENTOR(S):	Wyllie, Michael Grant
PATENT ASSIGNEE(S):	Pfizer Products Inc., USA

SOURCE: Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1123705	A1	20010816	EP 2001-301085	20010207 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 200100586	A2	20011128	HU 2001-586	20010206 <--
ZA 2001001012	A	20020806	ZA 2001-1012	20010206 <--
CA 2334460	A1	20010809	CA 2001-2334460	20010207 <--
US 2001044438	A1	20011122	US 2001-778290	20010207 <--
NZ 509807	A	20020927	NZ 2001-509807	20010208 <--
KR 2004032141	A	20040414	KR 2004-20671	20040326
US 2005222165	A1	20051006	US 2005-140723	20050531
US 7138405	B2	20061121		
AU 2006202176	A1	20060615	AU 2006-202176	20060523

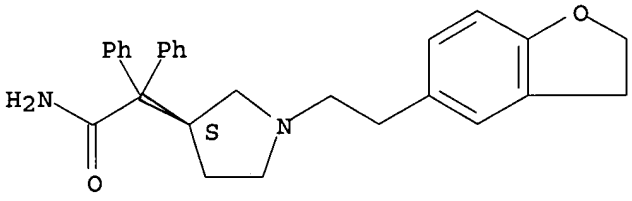
PRIORITY APPLN. INFO.:		
US 2000-181310P	P	20000209
AU 2001-18329	A3	20010207
US 2001-778290	A1	20010207
KR 2001-6417	A3	20010209

AB Pharmaceutical combinations suitable for treating the lower urinary tract symptoms associated with benign prostatic hyperplasia in men contain an α-adrenoceptor antagonist and a muscarinic antagonist. The combinations of the invention are particularly suitable for treating moderate or severe lower urinary tract symptoms. Thus, tablet contained doxazosin mesylate 4.05, microcryst. cellulose 125.28, lactose 66.67, sodium starch glycolate 2.00, and Mg stearate 2.00% by weight

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical combinations for treating lower urinary tract disfunctions)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

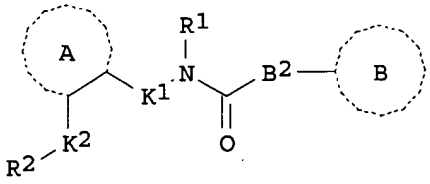
L19 ANSWER 37 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:46100 CA
TITLE: Preparation of 2-biphenyl 4-piperidinyl ureas having muscarinic receptor antagonist activity
INVENTOR(S): Mammen, Mathai; Oare, David
PATENT ASSIGNEE(S): Advanced Medicine, Inc., USA

SOURCE: PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 31
PATENT INFORMATION:

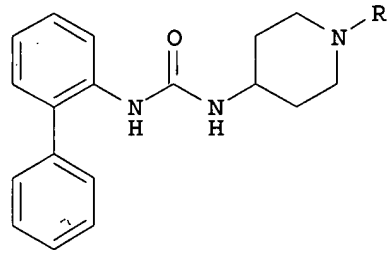
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2001042213	A1	20010614	WO 2000-US33155	20001207	<--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6693202	B1	20040217	US 2000-645609	20000825	
CA 2392030	A1	20010614	CA 2000-2392030	20001207	<--
BR 2000015963	A	20020806	BR 2000-15963	20001207	<--
EP 1235803	A1	20020904	EP 2000-982493	20001207	<--
EP 1235803	B1	20040714			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
HU 200203677	A2	20030328	HU 2002-3677	20001207	<--
JP 2003516391	T	20030513	JP 2001-543514	20001207	<--
NZ 518722	A	20040326	NZ 2000-518722	20001207	
AT 271039	T	20040715	AT 2000-982493	20001207	
EP 1457488	A1	20040915	EP 2004-12859	20001207	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
ES 2225275	T3	20050316	ES 2000-982493	20001207	
AU 782232	B2	20050714	AU 2001-19518	20001207	
ES 2243333	T3	20051201	ES 2000-983991	20001207	
NO 2002002683	A	20020702	NO 2002-2683	20020606	<--
ZA 2002004553	A	20030908	ZA 2002-4553	20020606	<--
ZA 2002004557	A	20030908	ZA 2002-4557	20020606	<--
HK 1049483	A1	20050218	HK 2003-101572	20030303	
US 2004110229	A1	20040610	US 2003-425368	20030429	

PRIORITY APPLN. INFO.:		
US 1999-456170	A2	19991207
US 1999-120287P	P	19990216
US 1999-325725	B2	19990604
US 2000-645609	A1	20000825
EP 2000-982493	A3	20001207
WO 2000-US33155	W	20001207

OTHER SOURCE(S): MARPAT 135:46100
GI



II



III

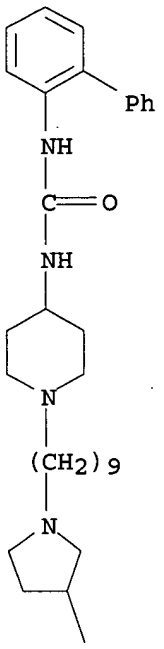
AB The title compds. L1XL2 [I; L1 = II (wherein A = (hetero)aryl; B2 = NRa; Ra = H, alkyl, etc.; R1 = H, alkyl; R2 = heteroaryl, etc.; K1 = a bond, alkylene; K2 = a bond, CO, SOn, etc.; n = 0-2; B = heterocycloamino, heteroarylamino); X = a linker; L2 = an organic group comprising at least one primary, secondary, or tertiary amine] which are muscarinic receptor antagonists and agonists (biol. data given), were prepared and formulated. E.g., a 2-step preparation of the intermediate III [R = H] starting with biphenyl-2-isocyanate and 4-amino-N-benzylpiperidine, was given. Mass spec data for 643 compds. III [R = XL2] were presented.

IT 344433-58-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2-biphenyl 4-piperidinyl ureas having muscarinic receptor antagonist activity)

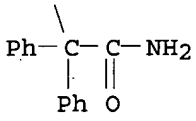
RN 344433-58-5 CA

CN 3-Pyrrolidineacetamide, 1-[9-[4-[[([1,1'-biphenyl]-2-ylamino)carbonyl]amino]-1-piperidinyl]nonyl]-α,α-diphenyl- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 38 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:29361 CA
TITLE: Molecular and pharmacological characterization of muscarinic receptor subtypes in a rat parotid gland cell line: comparison with native parotid gland
AUTHOR(S): Bockman, Charles S.; Bradley, Michael E.; Dang, Herbert K.; Zeng, Wanyun; Scofield, Margaret A.; Dowd, Frank J.
CORPORATE SOURCE: Department of Pharmacology, Creighton University School of Medicine, Omaha, NE, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 297(2), 718-726
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mol. and pharmacol. characteristics of muscarinic receptor subtypes in the rat parotid acinar cell line, PAR-C5, were determined and compared with

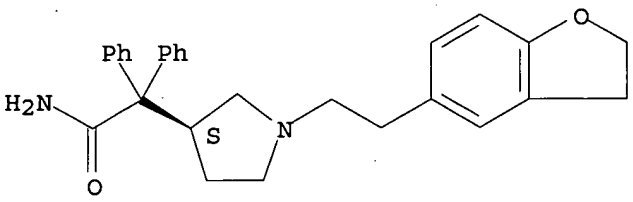
native rat parotid glands to evaluate the PAR-C5 cell line as a model to study receptor-mediated secretion. Reverse transcription-polymerase chain reaction (RT-PCR) identified mRNAs for M3, M4, and M5 receptor subtypes in both PAR-C5 cells and parotid glands. Specific [N-methyl-3H]scopolamine binding in PAR-C5 and parotid membranes was to a single class of sites with mean KD values of 0.38 and 0.64 nM, resp. Binding affinities (KI values) of muscarinic receptor subtype-selective drugs were obtained in side-by-side expts. comparing PAR-C5 cells with parotid glands. Nonlinear regression anal. indicated that competition binding curves for drugs in PAR-C5 cells and parotid glands fit best to a one-site binding model. KI values (nM) in PAR-C5 cells and parotid glands, resp., for atropine (1.0, 2.1), darifenacin (1.2, 2.0), 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP) (2.9, 2.4), tripitramine (220, 180), pirenzepine (320, 720), and methoctramine (1400, 1700) were consistent with their known affinities at the M3 receptor subtype. Affinities (KB values) of muscarinic receptor subtype-selective drugs for blocking methacholine-stimulated Ca2+ mobilization were determined to show which subtype mediates Ca2+-dependent secretion in Fura-2-loaded PAR-C5 cells. KB values (nM) for atropine (0.44), 4-DAMP (0.38), pirenzepine (140), and methoctramine (320) for blocking Ca2+ responses correlated well with their known affinities at the M3 receptor (r2 = 0.99). These results show that at the level of mRNA, receptor protein and function, PAR-C5 cells and parotid glands are similar, establishing PAR-C5 cells as an important model for muscarinic receptor-mediated secretion.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(muscarinic receptor subtype pharmacol. and functional characterization and expression in rat parotid gland cell line)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 39 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 134:348477 CA

TITLE: Functional characterization of rat submaxillary gland muscarinic receptors using microphysiometry

AUTHOR(S): Meloy, Trena D.; Daniels, Donald V.; Hegde, Sharath S.; Eglen, Richard M.; Ford, Anthony P. D. W.

CORPORATE SOURCE: Neurobiology Unit, Roche Bioscience, Palo Alto, CA, 94304, USA

SOURCE: British Journal of Pharmacology (2001), 132(7), 1606-1614
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

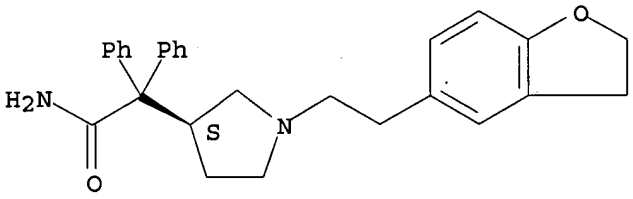
AB Muscarinic cholinoceptors (MChR) in freshly dispersed rat salivary gland (RSG) cells were characterized using microphysiometry to measure changes in acidification rates. Several non-selective and selective muscarinic antagonists were used to elucidate the nature of the subtypes mediating the response to carbachol. The effects of carbachol (pEC50 = 5.74±0.02 s.e.mean; n = 53) were highly reproducible and most antagonists acted in a surmountable, reversible fashion. The following antagonist rank order, with apparent affinity consts. in parentheses, was noted: 4-DAMP (8.9) = atropine (8.9) > tolterodine (8.5) > oxybutynin (7.9) > S-secoverine (7.2) > pirenzepine (6.9) > himbacine (6.8) > AQ-RA 741 (6.6) > methoctramine (5.9). These studies validate the use of primary isolated RSG cells in microphysiometry for pharmacol. anal. These data are consistent with, and extend, previous studies using alternative functional methods, which reported a lack of differential receptor pharmacol. between bladder and salivary gland tissue. The antagonist affinity profile significantly correlated with the profile at human recombinant muscarinic M3 and M5 receptors. Given a lack of antagonists that discriminate between M3 and M5, definitive conclusion of which subtype(s) is present within RSG cells cannot be determined

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(functional characterization of rat submaxillary gland muscarinic receptors using microphysiometry and receptor antagonists)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 40 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 134:247264 CA

TITLE: Treatment of lower urinary tract symptoms with muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors, and pharmaceutical compositions for use therein

INVENTOR(S): Stoner, Elizabeth; Drake, Paul J.; Bach, Mark A.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001021167	A1	20010329	WO 2000-US25534	20000918 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-155357P P 19990922

OTHER SOURCE(S): MARPAT 134:247264

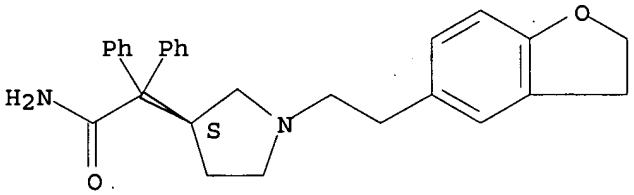
AB A medical condition in men known as Lower Urinary Tract Symptoms (LUTS) is treated by the administration of a muscarinic receptor antagonist in combination with at least one of a 5α-reductase inhibitor and an α-adrenergic receptor blocker.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors for treatment of lower urinary tract symptoms, and pharmaceutical compns.)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 41 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 134:232135 CA

TITLE: Pharmacological characterization of muscarinic receptors in dog isolated ciliary and urinary bladder smooth muscle

AUTHOR(S): Choppin, A.; Eglen, R. M.

CORPORATE SOURCE: Genitourinary-Pharmacology, Neurobiology Unit, Roche Bioscience, Palo Alto, CA, 94304, USA

SOURCE: British Journal of Pharmacology (2001), 132(4), 835-842
CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pharmacol. characteristics of muscarinic receptors mediating contraction of dog isolated ciliary muscle were determined and compared to those mediating contraction of dog urinary bladder smooth muscle. (+)-Cis-dioxolane induced concentration-dependent contractions of ciliary muscle

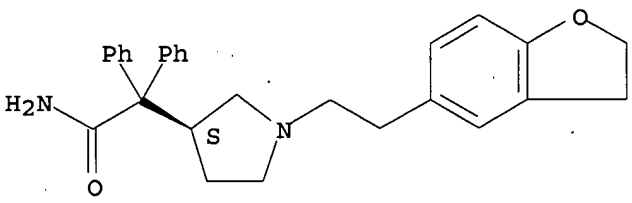
(pEC50 = 7.18, Emax = 453 mg) and urinary bladder isolated smooth muscle (pEC50 = 6.55, Emax = 11 g). These responses were antagonized by several muscarinic receptor antagonists (pKb values for the ciliary muscle and the bladder smooth muscle, resp.): atropine (8.25 and 9.21), pirenzepine (6.31 and 6.70), tolterodine (7.97 and 8.68), oxybutynin (7.40 and 7.88), zamifenacin (6.46 and 7.69), S-secoverine (6.66 and 8.13), AQ-RA 741 (6.16 and 7.08), p-F-HHSiD (7.10 and 7.35) and responses were not antagonized by PD 102807 (up to 100 nM). In urinary bladder smooth muscle, the profile of antagonist pKB values correlated significantly with pKi values at human recombinant m3 muscarinic receptors, suggesting that M3 muscarinic receptors mediated the response. In the ciliary muscle, a significant correlation was obtained with human recombinant m3 and m5 receptors. Darifenacin displayed insurmountable antagonism at receptors in the bladder. At receptors in the ciliary muscle, it exhibited two phases of antagonism, comprising an initial low affinity (pKB<6) component and a high affinity phase (pKB>8). The role of pigmentation in the atypical behavior of darifenacin was examined In blue colored eyes, darifenacin produced apparent surmountable, competitive antagonism of the responses to (+)-cis-dioxolane (pKB = 8.76). The antagonist profile obtained in this tissue suggested the involvement of a site which has the pharmacol. attributes of the M5 receptor. We suggest that the dog urinary bladder contracts in response to M3 muscarinic receptor activation. Contraction of the brown-eyed dog ciliary muscle is more complex and may include involvement of at least two receptors, possibly the M5 and M3 receptor, whereas blue-eyed dog ciliary muscle may involve a single population of M5 muscarinic receptors.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(eye pigmentation effect on darifenacin antagonism of muscarinic receptor-mediated ciliary muscle contraction in dogs)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 42 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 134:51792 CA

TITLE: The role of M2-muscarinic receptors in mediating contraction of the pig urinary bladder in vitro

AUTHOR(S): Yamanishi, Tomonori; Chapple, Christopher R.; Yasuda, Kosaku; Chess-Williams, Russell

CORPORATE SOURCE: Department of Biomedical Science, University of Sheffield, Sheffield, S10 2TN, UK

SOURCE: British Journal of Pharmacology (2000), 131(7), 1482-1488

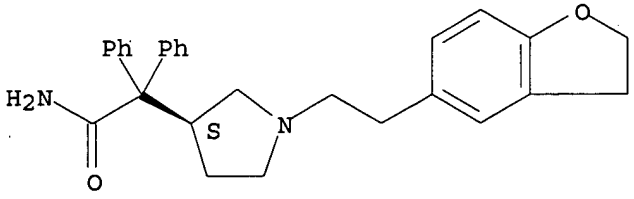
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In urinary bladder, M2-muscarinic receptors predominate, but it is the smaller population of M3-receptors which mediate detrusor contraction. This study examines the M2:M3 ratio and the role of M2-receptors in contraction of pig urinary bladder. Competition expts. with [3H]-QNB determined the ratio of M2:M3. In functional studies, affinity values (pKB) for 4-DAMP, darifenacin and methoctramine were calculated Similar expts. were performed on tissues following selective M3-inactivation (incubation with 40 nM 4-DAMP mustard in the presence of 1 μM methoctramine to protect M2-receptors), precontraction with 50 mM KCl and relaxation with isoprenaline (30 μM) or forskolin (1 μM). In competition binding, displacement of [3H]-QNB by 4-DAMP, darifenacin and methoctramine best fitted a two-site model suggesting a predominant (70-80%) population of M2-receptors. On normal detrusor in vitro, 4-DAMP and methoctramine caused surmountable antagonism of responses to carbachol with pKB values of 9.37 and 6.05 resp. Darifenacin caused unsurmountable antagonism, the apparent pKB value being 8.61. In tissues where the M3-receptors had been inactivated and cAMP levels elevated, 4-DAMP and darifenacin were less potent, with apparent pKB values of 8.72 and 6.74. In contrast, methoctramine was more potent, the apparent pKB value increasing significantly to 6.86. These data suggest that the pig bladder possesses a similar muscarinic receptor population to the human bladder and that the M3-receptor subtype mediates contraction of the normal detrusor muscle. However an involvement of M2-receptors in contraction can be observed following pharmacol. manipulation of the receptor population.

IT 133099-04-4, Darifenacin
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(M2-muscarinic receptors role in mediating contraction of pig urinary bladder in vitro)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 43 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:50809 CA
TITLE: Fast, generic gradient high performance liquid chromatography coupled to Fourier transform ion cyclotron resonance mass spectrometry for the accurate mass analysis of mixtures
AUTHOR(S): Speir, J. Paul; Perkins, George; Berg, Christian; Pullen, Frank

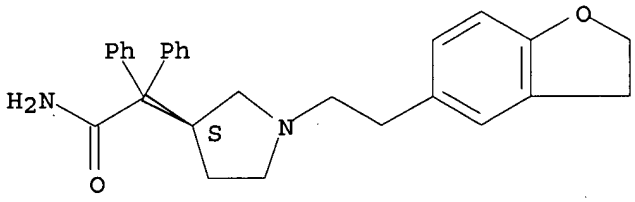
CORPORATE SOURCE: Bruker Daltonics, Inc., Billerica, MA, 01821, USA
SOURCE: Rapid Communications in Mass Spectrometry (2000), 14(20), 1937-1942
CODEN: RCMSEF; ISSN: 0951-4198
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fast gradient HPLC was combined with a com. available Fourier transform ICR (FTICR) mass spectrometer for the routine and high performance anal. of mixts. With this combination the authors were able to sep. and detect, under high mass accuracy conditions, a six-component drug mixture in <5 min. The fast gradients described are now possible due to the development of mech. robust, ultra pure silica packing materials, which allow relatively high flow rates (.apprx.1 mL/min for a 2 mm diameter column). For the six compds. present in the model mixture, relative mass errors of <1 ppm were obtained (based on an external calibration) providing sufficient mass accuracy to make unequivocal assignments of empirical formulas. Preliminary results of fast gradient HPLC/FTICR-MS/MS are also shown for the same six-component mixture

IT 133099-04-4
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(analyte; fast, generic gradient high performance liquid chromatog. coupled to Fourier transform ion cyclotron resonance mass spectrometry for accurate mass anal. of mixts.)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 44 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 132:58665 CA

TITLE: Synthesis and properties of molecular imprints of darifenacin: the potential of molecular imprinting for bioanalysis

AUTHOR(S): Venn, R. F.; Goody, R. J.
CORPORATE SOURCE: Department of Drug Metabolism, Pfizer Central Research, Kent, CT13 9NJ, UK

SOURCE: Chromatographia (1999), 50(7/8), 407-414
CODEN: CHRGB7; ISSN: 0009-5893
PUBLISHER: Friedrich Vieweg & Sohn Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English

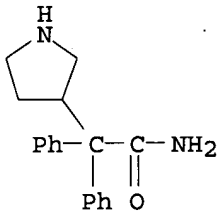
AB A molecularly imprinted polymer has been developed which subsequently demonstrated an ability to selectively retain darifenacin (UK-88, 525-S) from aqueous acetonitrile when used as a stationary phase in HPLC columns and as a packing in solid-phase extraction cartridges. The imprinted polymer is applicable to a wide range of anal. methods including extraction from plasma,

purification of radiolabeled UK-88,525, chiral sepns. and separation of metabolites
and structural analogs. The polymer is able to extract darifenacin directly from a protein-precipitated human plasma/acetonitrile (1:1 volume/volume) mixture with
100% recovery. The imprinted polymer can also effect a repurifn. of 14C-labeled darifenacin. The drawbacks of mol. imprints for ultra-trace bioanal. (in the sub-nanogram/mL range) are discussed. These center on the difficulty of removing all the template from the polymer and the consequent effects of template bleed on assay precision and accuracy when used as solid-phase extraction cartridges. Possible solns. to this problem are considered.

IT 103887-32-7, UK 88862
RL: ANT (Analyte); ANST (Analytical study)
(synthesis and properties of mol. imprints of darifenacin and potential of mol. imprinting for bioanal.)

RN 103887-32-7 CA

CN 3-Pyrrolidineacetamide, α,α-diphenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 45 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 132:35613 CA

TITLE: Muscarinic receptor antagonists

INVENTOR(S): Mammen, Mathai; Oare, David; Griffin, John H.; Aggen, James

PATENT ASSIGNEE(S): Advanced Medicine, Inc., USA

SOURCE: PCT Int. Appl., 181 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 31

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964043	A1	19991216	WO 1999-US12733	19990607 <--
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AU 9945491 A 19991230 AU 1999-45491 19990607 <--
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EP 1019360 A1 20000719 EP 1999-930123 19990607 <--
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EP 1085887 A2 20010328 EP 1999-928349 19990607 <--
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JP 2002517459 T 20020618 JP 2000-553102 19990607 <--
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EP 1082289	A1	20010314	EP 1999-930185		19990608 <--
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ZA 2000004085	A	20011112	ZA 2000-4085		20000810 <--
ZA 2000004087	A	20011113	ZA 2000-4087		20000810 <--
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US 6693202	B1	20040217	US 2000-645609		20000825
ZA 2000004561	A	20011130	ZA 2000-4561		20000831 <--
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US 2003087306	A1	20030508	US 2001-15534		20011213 <--
US 2004110229	A1	20040610	US 2003-425368		20030429
PRIORITY APPLN. INFO.:			US 1998-88466P	P	19980608
			US 1998-92938P	P	19980715
			US 1999-120287P	P	19990216
			US 1999-325725	B2	19990604
			WO 1999-US11786	W	19990604
			US 1999-327044	B1	19990607
			WO 1999-US11803	W	19990607
			WO 1999-US11805	W	19990607
			WO 1999-US12669	W	19990607
			WO 1999-US12673	W	19990607
			WO 1999-US12727	W	19990607
			WO 1999-US12728	W	19990607
			WO 1999-US12730	W	19990607

WO 1999-US12731	W	19990607
WO 1999-US12733	W	19990607
WO 1999-US12778	W	19990607
WO 1999-US12782	W	19990607
US 1999-327904	B1	19990608
WO 1999-US12626	W	19990608
WO 1999-US12770	W	19990608
WO 1999-US12876	W	19990608
WO 1999-US12907	W	19990608
WO 1999-US12989	W	19990608
WO 1999-US12994	W	19990608
WO 1999-US12995	W	19990608
US 1999-456170	B1	19991207
US 2000-493462	B1	20000128
US 2000-645609	A1	20000825

OTHER SOURCE(S): CASREACT 132:35613; MARPAT 132:35613

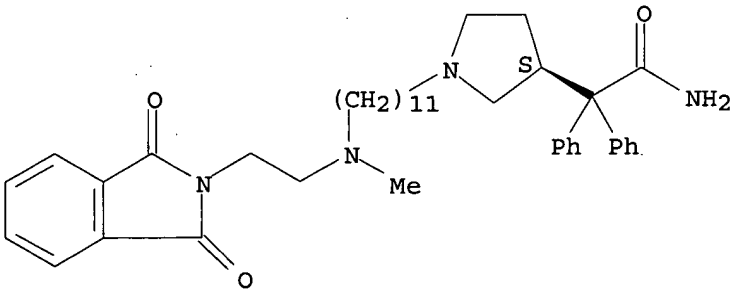
AB Title antagonists, comprising multibinding compds. containing 2-10 ligands covalently attached to ≥1 linkers, were prepared (no data). Each ligand is a muscarinic receptor antagonist or an allosteric modulator provided that ≥1 of said ligands is a muscarinic receptor antagonist. Thus, N-(2-dimethylaminoethyl)phthalimide (preparation given) was condensed with 2,6-bis(bromomethyl)pyridine to give, e.g., 2,6-bis[[(2-phthalimidoethyl)dimethylammonium]methyl]pyridine.

IT 252302-76-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(muscarinic receptor antagonists)

RN 252302-76-4 CA

CN 3-Pyrrolidineacetamide, 1-[11-[[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]methylamino]undecyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 46 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 131:138852 CA

TITLE: Pharmacodynamics of anticholinergic agents measured by ambulatory urodynamic monitoring: A study of methodology

AUTHOR(S): Rosario, Derek J.; Smith, David J.; Radley, Stephen C.; Chapple, Christopher R.

CORPORATE SOURCE: Department of Urology, Royal Hallamshire Hospital, Sheffield, S10 5FD, UK

SOURCE: Neurourology and Urodynamics (1999), 18(3),

223-234
CODEN: NEUREM; ISSN: 0733-2467
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

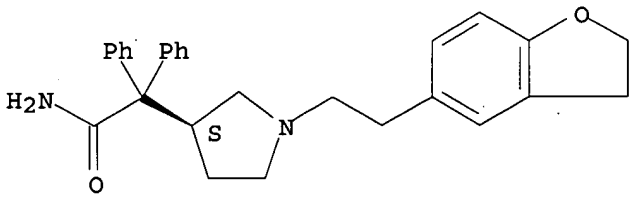
AB The aim of the study was to establish a methodol. whereby ambulatory urodynamic monitoring (AUM) may be used in the assessment of the effects of darifenacin on urodynamic measures of detrusor function and symptoms associated with detrusor instability. Six patients (one man and five women) with detrusor instability (DI) on conventional urodynamic monitoring were recruited into this placebo-controlled crossover study. The study was divided into two periods of 7 days of treatment with either darifenacin 5 mg t.d.s. or placebo with the patient crossing over to the alternative treatment after a washout period of 7 days. On the 7th day of each treatment, AUM was carried out. Parameters used to quantify detrusor activity on AUM were the number, amplitude, and duration of detrusor contractions and the total area under the detrusor pressure/time curve. "Events" recorded were urge, leakage episodes, voids, and pain. Six comparable hours of AUM for each treatment period could be analyzed in four patients and 4 h in one. In three of the five patients, reduction in activity on AUM while on darifenacin was apparent. Symptom data closely matched the changes in detrusor activity measured on AUM. This is the first study reporting the use of AUM in the development of a drug with an effect on detrusor activity. AUM has clear advantages over conventional cystometry, which can only measure surrogate urodynamic parameters at a single time point. The optimal duration of monitoring in this context appears to be 6 h with prolongation of monitoring time beyond this being unlikely to yield addnl. useful information. Correlation between symptoms and findings on AUM is good with changes in parameters recorded on AUM relating closely to the improvement in symptoms.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ambulatory urodynamic monitoring as a method for development of drugs for detrusor instability)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 47 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:125807 CA
TITLE: Comparative pharmacology of recombinant human M3 and M5 muscarinic receptors expressed in CHO-K1 cells
AUTHOR(S): Watson, Nikki; Daniels, Donald V.; Ford, Anthony P. D. W.; Eglen, Richard M.; Hegde, Sharath S.

CORPORATE SOURCE: Urogenital Pharmacology, Neurobiology Unit, Center for Biological Research, Palo Alto, CA, 94304, USA
SOURCE: British Journal of Pharmacology (1999), 127(2), 590-596
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

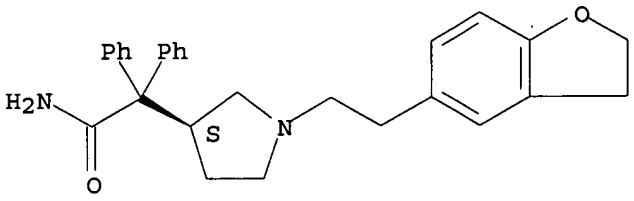
AB Affinity ests. were obtained for several muscarinic antagonists against carbachol-stimulated [3H]-inositol phosphates accumulation in Chinese hamster ovary (CHO-K1) cells stably expressing either human muscarinic M3 or M5 receptor subtypes. The rationale for these studies was to generate a functional antagonist affinity profile for the M5 receptor subtype and compare this with that of the M3 receptor, in order to identify compds. which discriminate between these two subtypes. The rank order of antagonist apparent affinities (pKB) at the muscarinic M5 receptor was atropine (8.7) ≥ tolterodine (8.6) = 4-diphenylacetoxy-N-methylpiperidine (4-DAMP, 8.6) > darifenacin (7.7) ≥ zamifenacin (7.6) > oxybutynin (6.6) = para-fluorohexahydrosiladifenidol (p-F-HHSiD, 6.6) > pirenzepine (6.4) ≥ methoctramine (6.3) = himbacine (6.3) > AQ-RA 741 (6.1). Antagonist apparent affinities for both receptor subtypes compare well with published binding affinity ests. No antagonist displayed greater selectivity for the muscarinic M5 subtype over the M3 subtype, but himbacine, AQ-RA 741, p-F-HHSiD, darifenacin and oxybutynin displayed between 9- and 60-fold greater selectivity for the muscarinic M3 over the M5 subtype. This study highlights the similarity in pharmacol. profiles of M3 and M5 receptor subtypes and identifies five antagonists that may represent useful tools for discriminating between these two subtypes. Collectively, these data show that in the absence of a high affinity M5 selective antagonist, affinity data for a large range of antagonists is critical to define operationally the M5 receptor subtype.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(recombinant human M3 and M5 muscarinic receptor comparative and discriminative pharmacol. after expression in CHO-K1 cells)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



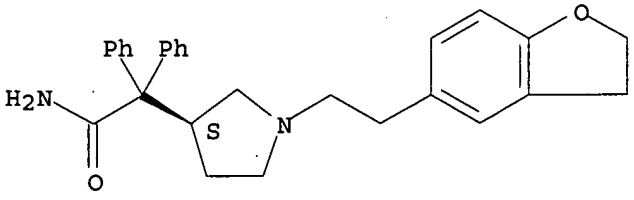
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 48 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:111728 CA
TITLE: Affinity profiles of various muscarinic antagonists for cloned human muscarinic acetylcholine receptor (mAChR) subtypes and mAChRs in rat heart and

submandibular gland

AUTHOR(S): Moriya, Hiroki; Takagi, Yoko; Nakanishi, Takahiro; Hayashi, Masatoshi; Tani, Tadato; Hirotsu, Ichiro
CORPORATE SOURCE: High Quality-Life Research Laboratories, Sumitomo Metal Industries, Ltd., Kyoto, 619-02, Japan
SOURCE: Life Sciences (1999), 64(25), 2351-2358
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A family of five subtypes of muscarinic acetylcholine receptors (mAChR) has been identified based on their mol. structures and second signal transduction pathways. In the present study, the authors examined the antagonist binding profiles of 9 muscarinic antagonists (atropine, 4-DAMP, pirenzepine, oxybutynin, tiquizium, timepidium, propiverine, darifenacin and zamifenacin) for human muscarinic acetylcholine receptor subtypes (m1, m2, m3, m4 and m5) produced by using a baculovirus infection system in Sf9 insect cells, and rat tissue membrane prepns. (heart and submandibular gland). In a scopolamine Me chloride [N-methyl-3H]- ([3H]NMS) binding assay, pirenzepine and timepidium displayed the highest affinities for the m1 and m2 subtypes, resp., and both zamifenacin and darifenacin had the highest affinities for the m3 subtype, although the selectivities among the five subtypes were less than 10-fold. Propiverine showed a slightly higher affinity for the m5 subtype, whereas none of the drugs used in this study was uniquely selective for the m4 subtype. The binding affinities of muscarinic antagonists for rat heart and submandibular gland strong correlated with those for human cloned m2 and m3 subtypes, resp. These data suggest that [3H]NMS binding studies using rat heart and submandibular gland might be useful methods which predict the affinities of test drugs for human muscarinic M2 and M3 receptor subtypes.
IT 133099-04-4, Darifenacin
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(affinity profiles of various muscarinic antagonists for cloned human muscarinic acetylcholine receptor subtypes and mAChRs in rat heart and submandibular gland)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 49 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:82422 CA
TITLE: Darifenacin Pfizer Inc
AUTHOR(S): Yoshiyama, M.
CORPORATE SOURCE: School of Medicine, Dept of Pharmacology, University

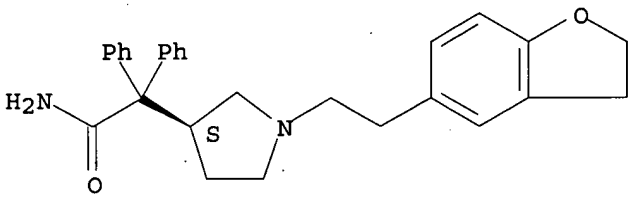
of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Current Opinion in Central & Peripheral Nervous System Investigational Drugs (1999), 1(2), 290-297
CODEN: COCDFA; ISSN: 1464-844X
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 47 refs., describing the pharmacol. of, darifenacin, a muscarinic antagonist in development by Pfizer. It is in phase III clin. trials for the treatment of urinary incontinence in the US. It reduces the frequency of incontinence within 1 wk and produces a dose-dependent increase in bladder capacity, similar to that given oxybutynin. It was also in phase III trials for use in irritable bowel syndrome. However, due to unsatisfactory results, the company decided to discontinue development for this indication in late 1998. Darifenacin is a muscarinic M3 antagonist that crosses the blood-brain barrier and is very lipophilic, but does not have any central-nervous side-effects. Darifenacin is a follow-up compound to zamifenacin which was discontinued during phase III trials.

IT 133099-04-4P, Darifenacin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(pharmacol. of muscarinic M3 antagonist darifenacin)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 50 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 130:261312 CA
TITLE: Muscarinic antagonists in development for disorders of smooth muscle function
AUTHOR(S): Wallis, Robert M.; Napier, Carolyn M.
CORPORATE SOURCE: Candidate Research Group, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK
SOURCE: Life Sciences (1999), 64(6/7), 395-401
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 19 refs. Compds. with high affinity for muscarinic M3 receptors have been used for many years to treat conditions associated with altered smooth muscle tone or contractility such as urinary urge incontinence, irritable bowel syndrome or chronic obstructive airways

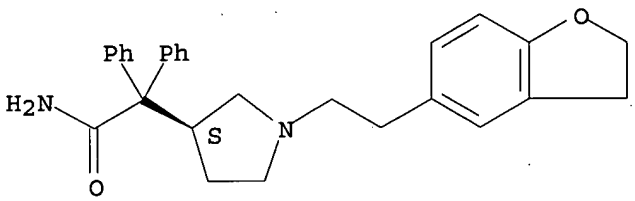
disease. M3 selective antagonists have the potential for improved toleration when compared with non-selective compds. Darifenacin has high affinity (pKi 9.12) and selectivity (9 to 74-fold) for the human cloned muscarinic M3 receptor. Consistent with this profile, the compound potently inhibited M3 receptor-mediated responses of smooth muscle prepns. (guinea pig ileum, trachea and bladder, pA2 8.66 to 9.4) with selectivity over responses mediated through the M1 (pA2 7.9) and M2 receptors (pA2 7.48). Interestingly, darifenacin also exhibited functional tissue selectivity for intestinal smooth muscle over the salivary gland. The M3 over M1 and M2 selectivity of darifenacin was confirmed in a range of animal models. In particular, in the conscious dog darifenacin inhibited intestinal motility at doses lower than those which inhibit gastric acid secretion (M1 response), increase heart rate (M2 response) or inhibit salivary secretion. Clin. studies are ongoing to determine if darifenacin has improved efficacy and or toleration when compared with non-selective agents.

IT 133099-04-4, Darifenacin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(muscarinic antagonist development for treatment of smooth muscle disorders)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 51 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 129:325658 CA

TITLE: Synthesis and properties of molecular imprints of darifenacin - does molecular imprinting have a future in ultra-trace bioanalysis?

AUTHOR(S): Venn, Richard F.; Goody, Robin J.

CORPORATE SOURCE: Department of Drug Metabolism, Pfizer Central Research, Kent, CT13 9NJ, UK

SOURCE: Methodological Surveys in Bioanalysis of Drugs (1998), 25(Drug Development Assay Approaches), 13-20
CODEN: MSBDE6

PUBLISHER: Royal Society of Chemistry

DOCUMENT TYPE: Journal

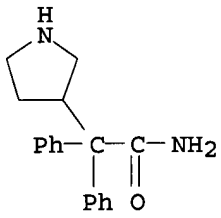
LANGUAGE: English

AB A molecularly imprinted polymer (MIP) was developed and was subsequently shown to be able to selectively retain darifenacin (UK 88,525 S) from aqueous MeCN when used a stationary phase in HPLC columns and as an SPE packing. The MIP's could distinguish between sep. sub-structures of the drug mol. as well as between the R- and S-enantiomers. A ring-opened metabolite was distinguishable from the parent, whereas the mono-hydroxylated metabolite

was not. The capacity for the drug was >100 μg per 100 mg polymer. The MIP could extract the drug directly, with 100% recovery, from human plasma deproteinized by MeCN (1 volume). Other applications of the MIP included repurifn. of 14C-labeled darifenacin. The drawbacks of MIP's for ultra-trace anal. are considered; they center on the difficulty of removing all the template from the polymer and the consequent effects of template bleed on assay precision and accuracy when the MIP is used as a solid phase extraction (SPE) cartridge. Possible solns. are discussed.

IT 103887-32-7, UK 88862
RL: ANT (Analyte); ANST (Analytical study)
(synthesis and properties of mol. imprints of darifenacin in relation to mol. imprinting in ultra-trace bioanal. of drugs in plasma)

RN 103887-32-7 CA
CN 3-Pyrrolidineacetamide, α,α-diphenyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 52 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 129:117709 CA
TITLE: Comparison of the in vitro and in vivo profiles of tolterodine with those of subtype-selective muscarinic receptor antagonists
AUTHOR(S): Gillberg, Per-Goran; Sundquist, Staffan; Nilvebrant, Lisbeth
CORPORATE SOURCE: Department of Pharmacology, Pharmacia and Upjohn, Uppsala, SE-752 81, Swed.
SOURCE: European Journal of Pharmacology (1998), 349(2/3), 285-292
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tolterodine [(R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine] is a new potent and competitive muscarinic receptor antagonist developed for the treatment of urinary urge incontinence and other symptoms of overactive bladder. In vivo, tolterodine exhibits functional selectivity for the urinary bladder over salivary glands, a profile that cannot be explained in terms of selectivity for a single muscarinic receptor subtype. The aim of this study was to compare the in vitro and in vivo antimuscarinic profiles of tolterodine with those of muscarinic receptor antagonists with distinct receptor subtype-selectivity profiles: darifenacin [(S)-2-{1-[2-(2,3-dihydrobenzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide; selective for muscarinic M3 receptors]; UH-AH 37 (6-chloro-5,10-dihydro-5-[(1-methyl-4-piperidinyl)acetyl]-11H-dibenzo-[b,e][1,4]diazepine-11-one; low affinity for muscarinic M2 receptors); and AQ-RA 741 (11-({4-[4-(diethylamino)butyl]-1-piperidinyl}acetyl)-5,11-dihydro-6H-pyrido[2,3-b][1,4]benzodiazepine-6-one; high affinity for muscarinic M2 receptors). The in vitro profiles of these compds. were in agreement with previous

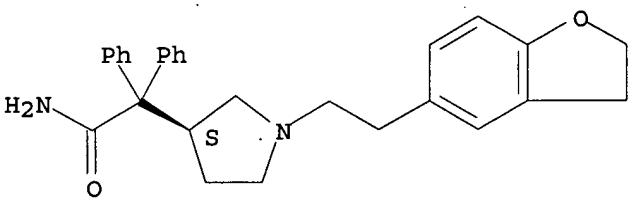
reports; darifenacin and UH-AH 37 demonstrated selectivity for muscarinic M3/m3 over M2/m2 receptors, while the converse was observed for AQ-RA 741. In vivo, AQ-RA 741 was more potent (1.4-2.7-fold) in inhibiting urinary bladder contraction than salivation in the anesthetized cat (i.e., a profile similar to that of tolterodine [2.5-3.3-fold]), while darifenacin and UH-AH 37 showed the reverse selectivity profile (0.6-0.8 and 0.4-0.5-fold, resp.). The results confirm that it is possible to sep. the antimuscarinic effects on urinary bladder and salivary glands in vivo. The data on UH-AH 37 and darifenacin support the view that a selectivity for muscarinic M3/m3 over M2/m2 receptors may result in a more pronounced effect on salivation than on bladder contraction. The data on AQ-RA 741 may indicate that muscarinic M2/m2 receptors may have a role in bladder contraction.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of the in vitro and in vivo profiles of tolterodine with those of subtype-selective muscarinic receptor antagonists)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 53 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 128:289686 CA

TITLE: Pharmacokinetics and metabolism of darifenacin in the mouse, rat, dog and man

AUTHOR(S): Beaumont, K. C.; Cussans, N. J.; Nichols, D. J.; Smith, D. A.

CORPORATE SOURCE: Department of Drug Metabolism and Early Clinical Research Group, Pfizer Central Research, Sandwich, CT13 9NJ, UK

SOURCE: Xenobiotica (1998), 28(1), 63-75
CODEN: XENOBH; ISSN: 0049-8254

PUBLISHER: Taylor & Francis Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Following i.v. administration to animals at 2·5 mg/kg, darifenacin exhibited terminal plasma half-lives < 2 h due to high plasma clearance (with respect to blood flow) and vols. of distribution greater than total body water. Following oral administration to animals at doses > 4 mg/kg, there was evidence of saturation of clearance since oral AUCs exceeded those expected from the high plasma clearances. In addition, terminal plasma half-lives were greater than those estimated from i.v. administration. In man, oral clearance was high with respect to liver blood flow. Following oral administration of the radiolabeled drug to animals and man, unchanged

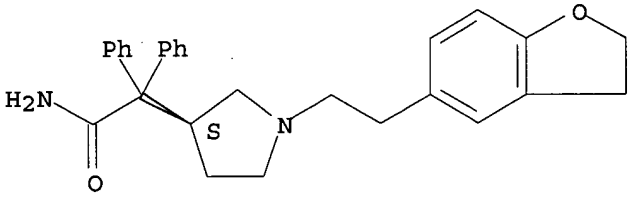
darifenacin was only a minor component of the fecal radioactivity indicating that darifenacin was well absorbed from. the gut. 5. Darifenacin was metabolized by three main routes in all species: monohydroxylation, oxidative dihydrobenzfuran ring opening and N-dealkylation. There were no marked species differences in the metabolism of darifenacin.

IT 133099-04-4, Darifenacin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics and metabolism of darifenacin in mouse and rat and dog and man)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 54 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 128:275083 CA

TITLE: Pharmaceutical compositions containing anti-incontinent agents

INVENTOR(S): Gast, Michael Jay; Koziol, Theodore Richard

PATENT ASSIGNEE(S): American Home Products Corporation, USA

SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9811888	A1	19980326	WO 1997-US16509	19970917 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2266070	A1	19980326	CA 1997-2266070	19970917 <--
AU 9744216	A	19980414	AU 1997-44216	19970917 <--
EP 927034	A1	19990707	EP 1997-942538	19970917 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
JP 2001502302	T	20010220	JP 1998-514847	19970917 <--
ZA 9708427	A	19990618	ZA 1997-8427	19970918 <--

PRIORITY APPLN. INFO.: US 1996-724263 A 19960919
WO 1997-US16509 W 19970917

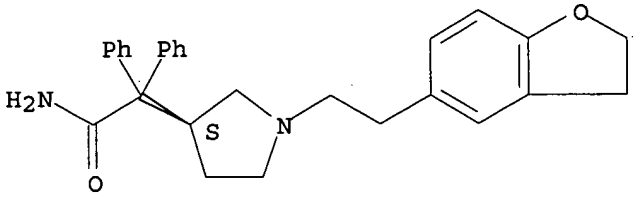
AB A method of treating urinary incontinence in a female mammal is provided which comprises administering to said mammal an effective amount of an anti-incontinent agent intravaginally or rectally. A solution of 16.67 g 3-ethoxy-4-(1,1-dimethylpropylamino)-cyclobut-3-ene-1,2-dione and 15.02 g 2,4-dichloro-6-methylbenzylamine in 395 mL ethanol was allowed to stand for 4 day at room temperature to form a white solid which was filtered, washed and dried, (yield 92%). A vaginal tablet contained imipramine hydrochloride 0.05, polycarbophil 0.5, lactose 0.4425, polyvinylpyrrolidone 0.005, and magnesium stearate 0.0025 g.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing anti-incontinent agents)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 55 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 128:97719 CA
TITLE: Use of darifenacin to enhance cognitive functions
INVENTOR(S): Allen, Michael John; Johnson, Brian Frank; Leaker, Brian Robert; Wallis, Robert Michael
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 813870	A1	19971229	EP 1997-303879	19970605 <--
EP 813870	B1	20030625		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 243514	T	20030715	AT 1997-303879	19970605 <--
PT 813870	T	20031031	PT 1997-303879	19970605 <--
ES 2197972	T3	20040116	ES 1997-303879	19970605
JP 10059848	A	19980303	JP 1997-151899	19970610 <--
JP 3453493	B2	20031006		
US 5837724	A	19981117	US 1997-872891	19970611 <--
CA 2208111	A1	19971218	CA 1997-2208111	19970616 <--

CA 2208111	C	20021015			
AU 9724956	A	19980108	AU 1997-24956		19970617 <--
ZA 9705311	A	19981217	ZA 1997-5311		19970617 <--
HU 9701060	A2	19981228	HU 1997-1060		19970617 <--
PRIORITY APPLN. INFO.:			GB 1996-12710	A	19960618

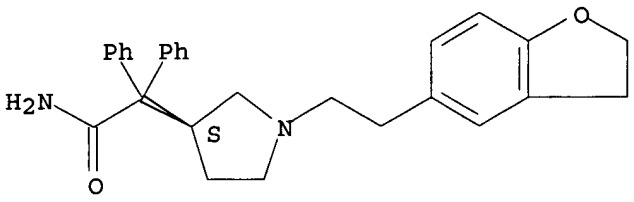
AB Darifenacin, and its pharmaceutically acceptable salts, are useful in the treatment of cognitive impairment. The invention also discloses the use of combinations of darifenacin, or a pharmaceutically acceptable salt thereof, with an acetylcholinesterase inhibitor (e.g. donepezil), in the treatment of cognitive impairment.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(darifenacin to enhance cognitive functions)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 56 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	127:55911 CA
TITLE:	Controlled-release pharmaceutical formulations containing low molecular weight polyethylene oxide and hydroxypropylmethyl cellulose
INVENTOR(S):	Macrae, Ross James; Smith, Janet Sarah
PATENT ASSIGNEE(S):	Pfizer Research and Development Company, N.V./s.A.La Touche Houseinternational Financial Services Centredublin 1, UK; Pfizer Inc.; Macrae, Ross James; Smith, Janet Sarah
SOURCE:	PCT Int. Appl., 20 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9718814	A1	19970529	WO 1996-EP5020	19961111 <--
W: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2232715	A1	19970529	CA 1996-2232715	19961111 <--
AU 9675721	A	19970611	AU 1996-75721	19961111 <--
AU 709560	B2	19990902		
EP 862437	A1	19980909	EP 1996-938215	19961111 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,				

	SI, LV, FI, RO					
JP 10513481	T	19981222	JP 1996-519364		19961111	<--
CN 1215993	A	19990505	CN 1996-198486		19961111	<--
BR 9611626	A	19990601	BR 1996-11626		19961111	<--
HU 9903734	A2	20000328	HU 1999-3734		19961111	<--
ZA 9609722	A	19980520	ZA 1996-9722		19961120	<--
NO 9802302	A	19980717	NO 1998-2302		19980520	<--
PRIORITY APPLN. INFO.:			GB 1995-23752	A	19951121	
			WO 1996-EP5020	W	19961111	

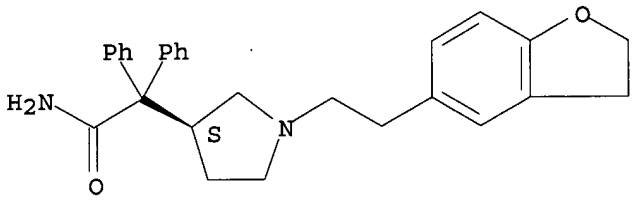
AB A controlled-release pharmaceutical formulation for oral administration consisting essentially of an active drug compound, low mol. weight polyethylene oxide (I), hydroxypropylmethyl cellulose (II), tableting excipients, and optionally one or more enteric polymers is claimed. Formulations according to the invention produce a constant rate of release of drug in in vivo models of the gastrointestinal tract. A sustained release tablet contained doxazosin mesylate 3.636, I (mol. weight = 100,000) 9.000, I (mol. weight 200,000) 9.000, II 60.000, dibasic calcium phosphate 58.182, lactose 58.182, and magnesium stearate 2.000 mg.

IT 133099-07-7, Darifenacin hydrobromide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release pharmaceutical formulations containing low mol. weight polyethylene oxide and hydroxypropylmethyl cellulose)

RN 133099-07-7 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, monohydrobromide, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HBr

L19 ANSWER 57 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	126:282826 CA
TITLE:	Pharmaceutical formulations containing darifenacin
INVENTOR(S):	Dolan, Thomas Francis; Humphrey, Michael John; Nichols, Donald John
PATENT ASSIGNEE(S):	Pfizer Research and Development Company, N.V./S.A., Ire.; Pfizer Limited; Pfizer Inc.
SOURCE:	PCT Int. Appl., 19 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9709980	A1	19970320	WO 1996-EP3719	19960821 <--
W: AU, BR, CA, CN, CU, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SG,				

TR, US, VN
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

TW 442300	B	20010623	TW 1996-85109518	19960806	<--
CA 2230314	A1	19970320	CA 1996-2230314	19960821	<--
CA 2230314	C	20030624			
AU 9669275	A	19970401	AU 1996-69275	19960821	<--
AU 703866	B2	19990401			
EP 850059	A1	19980701	EP 1996-930085	19960821	<--
EP 850059	B1	20030226			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

CN 1195984	A	19981014	CN 1996-196977	19960821	<--
JP 10511112	T	19981027	JP 1997-511602	19960821	<--
JP 3403203	B2	20030506			
BR 9610153	A	19990105	BR 1996-10153	19960821	<--
IL 122746	A	20001206	IL 1996-122746	19960821	<--
RU 2163803	C2	20010310	RU 1998-107322	19960821	<--
EP 1245231	A2	20021002	EP 2002-15165	19960821	<--
EP 1245231	A3	20030115			
EP 1245231	B1	20040616			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

AT 233090	T	20030315	AT 1996-930085	19960821	<--
PL 185604	B1	20030630	PL 1996-325598	19960821	<--
ES 2188782	T3	20030701	ES 1996-930085	19960821	<--
AT 269076	T	20040715	AT 2002-15165	19960821	
PT 1245231	T	20041029	PT 2002-15165	19960821	
ES 2224002	T3	20050301	ES 2002-15165	19960821	
ZA 9607745	A	19980313	ZA 1996-7745	19960913	<--
US 6106864	A	20000822	US 1998-29072	19980303	<--
NO 9801073	A	19980311	NO 1998-1073	19980311	<--
NO 314783	B1	20030526			
AU 9936884	A	19990826	AU 1999-36884	19990630	<--
AU 726814	B2	20001123			

PRIORITY APPLN. INFO.:	GB 1995-18953	A 19950915
	AU 1996-69275	A3 19960821
	EP 1996-930085	A3 19960821
	WO 1996-EP3719	W 19960821

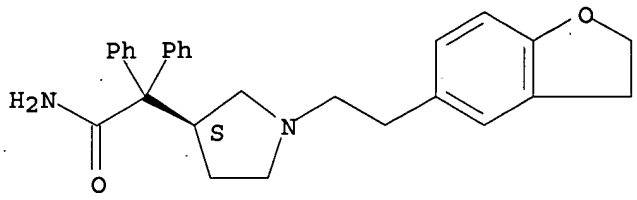
AB There is provided a pharmaceutical dosage form adapted for administration to the gastrointestinal tract of a patient, comprising darifenacin, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier; characterized in that the dosage form is adapted to deliver at least 10% by weight of the darifenacin, or the pharmaceutically acceptable salt thereof, to the lower gastrointestinal tract of the patient. The formulation minimizes unwanted side-effects and increases the bioavailability of darifenacin. An example formulation contained darifenacin hydrobromide, Methocel K4M, Methocel K100LV Premium, Fast-flo lactose, and Mg stearate.

IT 133099-04-4, Darifenacin
RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(darifenacin pharmaceuticals for gastrointestinal tract)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



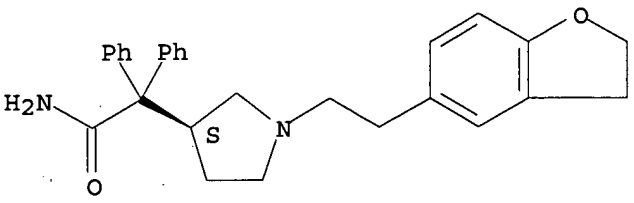
L19 ANSWER 58 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:272115 CA
TITLE: Discovery and development of selective M3 antagonists for clinical use
AUTHOR(S): Alabaster, V. A.
CORPORATE SOURCE: Dept. of Discovery Biology, Pfizer Central Research, Kent, CT13 9NJ, UK
SOURCE: Life Sciences (1997), 60(13/14), 1053-1060
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The treatment of airway obstructive disease may be improved by antimuscarinic agents which selectively block M1 and M3 receptors but do not inhibit prejunctional cholinergic autoreceptors which limit release of acetylcholine. Revatropate is a novel antimuscarinic agent which shows some 50-fold selectivity for M1 and M3 receptors in guinea pig trachea and rabbit vas deferens over the M2 subtype in atria. This selectivity profile was seen in vivo in anesthetized guinea pigs and conscious dogs where bronchodilator activity was produced in the absence of any effect on heart rate. Revatropate, in contrast to the non-selective agent ipratropium, did not potentiate bronchoconstrictor responses induced by vagal nerve stimulation, indicating that inhibitory autoreceptors were still functional. Early clin. studies in COAD patients showed that inhaled revatropate was an effective bronchodilator which was well tolerated. Darifenacin differs from revatropate by showing selectivity for M3 receptors relative to both M2 and M1 subtypes. [3H]darifenacin had 5-fold higher affinity for the human M3 relative to M1 receptors while there was significantly reduced binding to M2, M4 and M5 receptors. The degree of selectivity in functional tissue prepns. was even greater, with darifenacin showing 100-fold selectivity for the ileum M3 receptors over M2 receptors in atria and 30-fold over M1 receptors in rabbit vas deferens. Darifenacin was able to differentiate between M3 receptors in different tissues; although darifenacin was equipotent with atropine in the ileum and bladder, it was some 10-fold and 6-fold less potent at inhibiting muscarinic responses in the trachea and submandibular salivary gland resp., relative to atropine. Studies in anesthetized dogs confirmed this selectivity profile. Thus darifenacin inhibited responses of the gut and bladder to cholinergic stimulation without affecting heart rate. Salivary gland responses were inhibited at doses some 6-10 fold higher than those required to inhibit gut and bladder responses. Clin. studies are ongoing in urge incontinence and functional bowel disease which may confirm this selectivity profile.

IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development and subtype selectivity of muscarinic antagonists and clin. use)

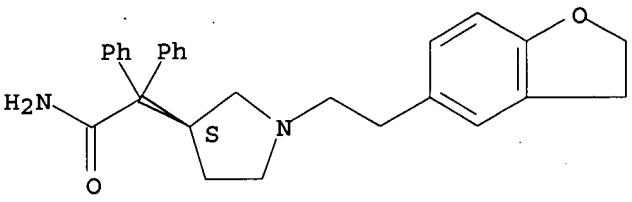
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



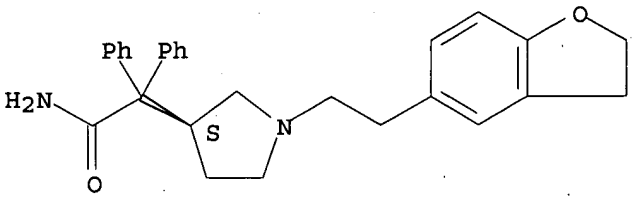
L19 ANSWER 59 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:195585 CA
TITLE: Characterization of [3H]-darifenacin as a novel radioligand for the study of muscarinic M3 receptors
AUTHOR(S): Smith, Carolyn M.; Wallis, Rob M.
CORPORATE SOURCE: Discovery Biology, Pfizer Central Research, Kent, CT13 9NJ, UK
SOURCE: Journal of Receptor and Signal Transduction Research (1997), 17(1-3), 177-184
CODEN: JRETET; ISSN: 1079-9893
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Darifenacin, (S)-2-[1-[2,3-dihydrobenzofuran-5-yl]-3-pyrrolidinyl]-2,2-diphenylacetamide, is a novel muscarinic M3 antagonist. In this study the authors have compared the binding of [3H]-darifenacin to the five cloned human muscarinic receptors (m1 - m5) expressed in CHO cells. [3H]-darifenacin binds with 6-fold higher affinity to m3 (KD = 0.33 nM) over m1 (KD = 1.6 nM) receptors. There was no specific binding of [3H]-darifenacin to m2 receptors and specific binding to m4 and m5 receptors was insufficient to determine a KD. Binding of [3H]-darifenacin to m1 and m3 was displaced by atropine (m1 pKi = 9.36, m3 pKi = 9.4), 4-DAMP (m1 pKi = 9.04, m3 pKi = 9.19), pirenzepine (m1 pKi = 8.63, m3 pKi = 6.85), methoctramine (m1 pKi = 7.28, m3 pKi = 6.63), and darifenacin (m1 pKi = 8.36, m3 pKi = 9.14), demonstrating that [3H]-darifenacin represents the first selective m3 radioligand.
IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
([3H]darifenacin as novel radioligand for study of muscarinic M3 receptors)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 60 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:139374 CA
TITLE: Darifenacin. Agent for irritable bowel syndrome and urinary incontinence, a muscarinic M3 antagonist
AUTHOR(S): Graul, A.; Castaner, J.
CORPORATE SOURCE: Prous Science Publishers, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (1996), 21(11), 1105-1108
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 12 refs., of the clin. pharmacol. of darifenacin for treatment of irritable bowel syndrome and urinary incontinence as a muscarinic M3 antagonist.
IT 133099-04-4, Darifenacin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(darifenacin. Agent for irritable bowel syndrome and urinary incontinence, a muscarinic M3 antagonist)
RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 61 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 124:225750 CA
TITLE: Rapid, Solid Phase Extraction Technique for the High-Throughput Assay of Darifenacin in Human Plasma
AUTHOR(S): Kaye, Barry; Herron, William J.; Macrae, Paul V.; Robinson, Sylvia; Stopher, David A.; Venn, Richard F.; Wild, William
CORPORATE SOURCE: Department of Drug Metabolism, Pfizer Central Research, Kent, CT13 9NJ, UK
SOURCE: Analytical Chemistry (1996), 68(9), 1658-60

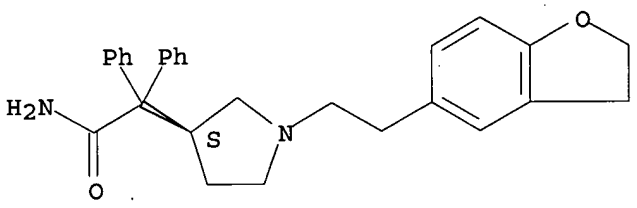
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel method has been developed for the rapid solid phase extraction of drugs and metabolites from biol. fluids, prior to further anal. The newly designed, 96-tube micropreparation block facilitates high throughput by enabling the extraction of 96 samples simultaneously. The system is described, linked to HPLC/APCI-MS/MS, for the determination of darifenacin in human plasma.
The resulting procedure, using deuterated darifenacin as internal standard, is validated over the concentration range 25-2000 pg/mL; accuracy (0.6-4.6%) and precision (3.6-18.8%) are considered acceptable and overall recovery was determined to be .apprx.50%.

IT 133099-04-4P, Darifenacin
RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); PUR (Purification or recovery); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(rapid, solid phase extraction technique for the high-throughput assay of darifenacin in human plasma)

RN 133099-04-4 CA
CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 62 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 123:160862 CA
TITLE: Use of muscarinic M3 antagonists for the treatment of motion sickness
INVENTOR(S): Rapeport, William Garth; Wallis, Robert Michael
PATENT ASSIGNEE(S): Pfizer Ltd., UK; Pfizer Research and Development Co. N.V./S.A.; Pfizer Inc.
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9519164	A1	19950720	WO 1995-EP44	19950104 <--
W: AU, CA, CN, FI, JP, KR, MX, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9514553	A	19950801	AU 1995-14553	19950104 <--
ZA 9500244	A	19960715	ZA 1995-244	19950113 <--

PRIORITY APPLN. INFO.: GB 1994-600 A 19940114
WO 1995-EP44 W 19950104

AB Motion sickness is treated or prevented by administration of M3-selective

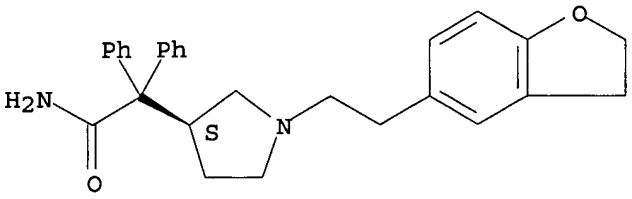
muscarinic receptor antagonists such as darifenacin (I). In a double-blind trial, it was found that the tolerance of nauseagenic motion was increased by both I and scopolamine; however, the heart rate was significantly reduced at 1 and 2 h post-administration of scopolamine, whereas no heart rate reduction occurred with I.

IT 133099-04-4, Darifenacin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(muscarinic M3 antagonists for treatment of motion sickness)

RN 133099-04-4 CA

CN 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-α,α-diphenyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 63 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 115:158959 CA

TITLE: Preparation of 3-(1-carbamoyl-1,1-diphenylmethyl)-1-(phenalkyl)pyrrolidines as muscarinic antagonists

INVENTOR(S): MacKenzie, Alexander Roderick; Cross, Peter Edward

PATENT ASSIGNEE(S): Pfizer Ltd., UK; Pfizer Inc.

SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

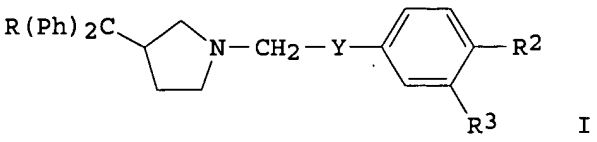
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9109013	A1	19910627	WO 1990-EP2043	19901128 <--
W: CA, FI, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
US 5340831	A	19940823	US 1990-859471	19900612 <--
CA 2069910	A1	19910613	CA 1990-2069910	19901128 <--
CA 2069910	C	19961112		
EP 505376	A1	19920930	EP 1990-917056	19901128 <--
EP 505376	B1	19941207		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 04505927	T	19921015	JP 1990-515786	19901128 <--
JP 06078303	B	19941005		
ES 2064771	T3	19950201	ES 1990-917056	19901128 <--
FI 9202345	A	19920522	FI 1992-2345	19920522 <--
FI 95027	B	19950831		
FI 95027	C	19951211		

PRIORITY APPLN. INFO.: GB 1989-28042 A 19891212
WO 1990-EP2043 W 19901128

OTHER SOURCE(S): MARPAT 115:158959

GI



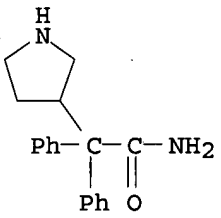
I

AB 3-(1-Carbamoyl-1,1-diphenylmethyl)-1-(phenalkyl)pyrrolidines I [Y = CH2, (CH2)2, CH2O, (CH2)2O, CH2S; R = cyano, CONH2; R2, R3 = H, C1-4 alkyl, C1-4 alkoxy, (CH2)nOH, halo, CF3, cyano, (CH2)nNR4R5, COR8, OCOR8, CHOHR8, COHR8R8, SO2NH2, (CH2)nCONR6R7, (CH2)nCO2R8; R4 = H, C1-4 alkyl; R5 = C1-4 alkyl, C1-4 alkylsulfonyl; R6, R7 = H, C1-4 alkyl; R8 = C1-4 alkyl; n = 0-2], useful as muscarinic antagonists (no data), were prepared Thus, 3-hydroxypyrrolidine was treated with TosCl and the ditosylate was condensed with Ph2CHC.tplbond.N in the presence of NaH to give 3-(1-cyano-1,1-diphenylmethyl)-1-tosylpyrrolidine. This was detosylated by aqueous HBr/PhOH, then hydrolyzed by 95% H2SO4 to give 3-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine. This was refluxed with 4-fluorophenethyl bromide in MeCN containing anhydrous K2CO3 to give title compound I (R = CONH2, R2 = F, R3 = H, Y = CH2).

IT 103887-32-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for muscarinic antagonists)

RN 103887-32-7 CA

CN 3-Pyrrolidineacetamide, α,α-diphenyl- (9CI) (CA INDEX NAME)



L19 ANSWER 64 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 114:247125 CA

TITLE: Preparation of pyrrolidine derivatives as muscarinic receptor antagonists

INVENTOR(S): Cross, Peter Edward; Mackenzie, Alexander Roderick

PATENT ASSIGNEE(S): Pfizer Ltd., UK; Pfizer Inc.

SOURCE: Eur. Pat. Appl., 33 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

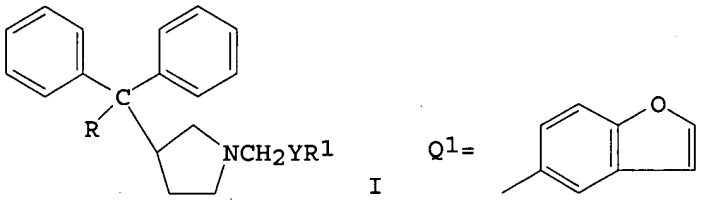
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 388054	A1	19900919	EP 1990-302269	19900302 <--
EP 388054	B1	19931103		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 96783	T	19931115	AT 1990-302269	19900302 <--
ES 2060020	T3	19941116	ES 1990-302269	19900302 <--

IL 93694	A	19940826	IL 1990-93694		19900309 <--
US 5096890	A	19920317	US 1990-493068		19900313 <--
US 5096890	B1	19950328			
HU 58313	A2	19920228	HU 1990-1580		19900314 <--
HU 217433	B	20000128			
CA 2012295	A1	19900917	CA 1990-2012295		19900315 <--
CA 2012295	C	19961112			
JP 02282360	A	19901119	JP 1990-65521		19900315 <--
JP 07064809	B	19950712			
ZA 9001982	A	19911030	ZA 1990-1982		19900315 <--
NO 9001241	A	19900918	NO 1990-1241		19900316 <--
NO 176316	B	19941205			
NO 176316	C	19950315			
AU 9051402	A	19900920	AU 1990-51402		19900316 <--
AU 614224	B2	19910822			
DD 292911	A5	19910814	DD 1990-338829		19900316 <--
SU 1833374	A3	19930807	SU 1990-4743599		19900316 <--
PL 164136	B1	19940630	PL 1990-284342		19900316 <--
CZ 280053	B6	19951018	CZ 1990-1295		19900316 <--
FI 95573	B	19951115	FI 1990-1333		19900316 <--
FI 95573	C	19960226			
SK 278434	B6	19970507	SK 1990-1295		19900316 <--
CN 1045580	A	19900926	CN 1990-101543		19900317 <--
CN 1023007	B	19931208			
RU 2015965	C1	19940715	RU 1991-4894696		19910313 <--
US 5233053	A	19930803	US 1992-800191		19920207 <--
JP 07149640	A	19950613	JP 1994-229807		19940926 <--
PRIORITY APPLN. INFO.:			GB 1989-6166	A	19890317
			EP 1990-302269	A	19900302
			US 1990-491068	A3	19900313

OTHER SOURCE(S): MARPAT 114:247125

GI



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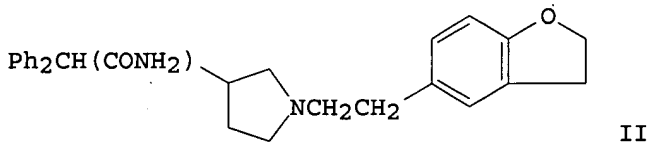


II

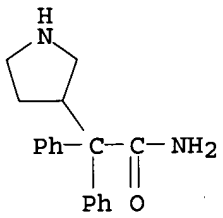
AB The title compds. I (Y = direct link, CH2, (CH2)2, CH2O, CH2S; R = CN, CONH2; R1 = Q1, pyridyl, pyrazinyl, etc.) were prepared I are useful as muscarinic receptor antagonists (no data). A mixture of 3-(R,S)-(1-carbamoyl-1,1-diphenylmethyl)pyrrolidine, 5-(2-bromoethyl)-2,3-dihydrobenzofuran and K2CO3 in MeCN was refluxed for 2 h to give pyrrolidine derivative (3R,S)-II.

IT 103887-32-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and reaction of, in preparation of muscarinic receptor antagonist)

RN 103887-32-7 CA
CN 3-Pyrrolidineacetamide, α,α-diphenyl- (9CI) (CA INDEX NAME)



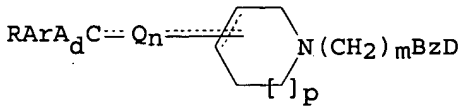
L19 ANSWER 65 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 108:37654 CA
TITLE: Preparation of N-aryloxyalkyl arylalkyl- and arylalkylenepiperidines as antihypertensives and antianginal agents
INVENTOR(S): Shanklin, James Robert, Jr.; Proakis, Anthony George
PATENT ASSIGNEE(S): A. H. Robins Co., Inc., USA
SOURCE: S. African, 184 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ZA 8604522	A	19870225	ZA 1986-4522	19860617 <--
IN 163948	A1	19881210	IN 1986-MA407	19860527 <--
IL 78939	A	19900429	IL 1986-78939	19860527 <--
JP 62169763	A	19870725	JP 1986-169673	19860718 <--
JP 07072171	B	19950802		
DK 8603479	A	19870718	DK 1986-3479	19860722 <--
AU 8662473	A	19870723	AU 1986-62473	19860909 <--
AU 594972	B2	19900322		
EP 228893	A2	19870715	EP 1986-310047	19861222 <--
EP 228893	A3	19900103		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
EP 235463	A2	19870909	EP 1986-310045	19861222 <--
EP 235463	A3	19900117		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1291995	C	19911112	CA 1987-526931	19870108 <--
AU 8929823	A	19890810	AU 1989-29823	19890210 <--
AU 629535	B2	19921008		
ZA 8901081	A	19901031	ZA 1989-1081	19890210 <--

PRIORITY APPLN. INFO.:

US 1986-819701	A	19860117
US 1988-154390		19880210
US 1985-811799	A	19851220
ZA 1986-4522		19860617

GI



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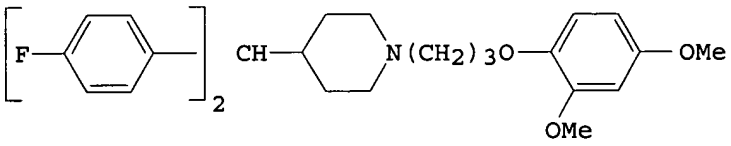


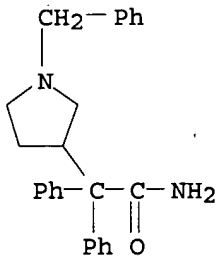
II

AB The title compds. I [A = H, OR1, cyano, CONR1R2, COR1, CO2R1, R1CO2, CH2OR1, CH2NR1R2; Ar = pyridyl, thienyl, furyl, naphthyl, (un)substituted Ph; B = O, S, SO, SO2, NR1, NCO2R1; D = Ar, benzopyranyl, benzodioxanylalkyl, quinolinyl; Q = CH, CH2, CHOH; R = Ar, (un)substituted PhCH2; R1 = H, R2; R2 = alkyl, Ph, phenylalkyl; d, n, z = 0, 1 (n + z ≠ 0); m = 0-6; p = 0-2] were prepared as antihypertensives and antianginal agents. A mixture of 4.75 g 4-[α,α-bis(p-fluorophenyl)methyl]piperidine and 4.0 g 3-(p-acetyl-o-methoxyphenoxy)propyl chloride (preparation each given) in DMF containing NaHCO3 was heated at 100° for 1 h to give 5.5 g disubstituted piperidine II which, at 10-7 M, caused a 100% reduction in contraction of rabbit aortal strips exposed to 10-3 M Ca.

IT 103887-42-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrogenolysis of, in preparation of antihypertensives and antianginal agents)

RN 103887-42-9 CA

CN 3-Pyrrolidineacetamide, α,α-diphenyl-1-(phenylmethyl)- (9CI) (CA INDEX NAME)



L19 ANSWER 66 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 105:114919 CA

TITLE: 1-(Aminoalkyl)-α,α-diarylpyrrolidine-, piperidine-, and homopiperidineacetamides and -acetonitriles

INVENTOR(S): Welstead, William John, Jr.

PATENT ASSIGNEE(S): A. H. Robins Co., Inc., USA

SOURCE: Eur. Pat. Appl., 58 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 178946	A2	19860423	EP 1985-307553	19851018 <--
EP 178946	A3	19880622		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
IL 76583	A	19880831	IL 1985-76583	19851004 <--
AU 8548906	A	19860424	AU 1985-48906	19851018 <--
AU 584930	B2	19890608		
JP 61100562	A	19860519	JP 1985-233166	19851018 <--
CA 1246564	A1	19881213	CA 1985-493339	19851018 <--
PRIORITY APPLN. INFO.:			US 1984-662584 A	19841019
OTHER SOURCE(S):	MARPAT 105:114919			

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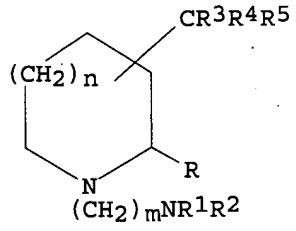

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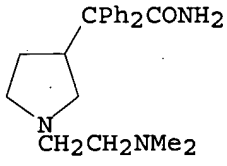


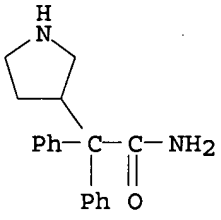
II

AB The title compds. [I; R = H, alkyl; R1, R2 = H, alkyl, (un)substituted Ph, phenylalkyl; R1R2N = pyrrolidino, morpholino, (un)substituted piperidino, piperazino; R3, R4 = pyridyl, (un)substituted Ph; R5 = aminocarbonyl, cyano; n = 0-2; m = 2-5] were prepared as antiarrhythmics. Thus, α,α-diphenyl-3-pyrrolidineacetamide was alkylated with ClCH2CH2NMe2 to give pyrrolidineacetamide II. In dogs 5.0 mg II/kg i.v. counteracted ouabain-induced arrhythmia. An i.v. injection contained 1.0 mg II and sterile pH 4.0 buffer to 1 mL.

IT 103913-15-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation of, with (diethylamino)ethyl chloride)

RN 103913-15-1 CA

CN 3-Pyrrolidineacetamide, α,α-diphenyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L19 ANSWER 67 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 105:114918 CA

TITLE: 1-[(Aminoalkyl- and aminoalkylamino)carbonyl- and -thiocarbonyl]-α,α-diarylpyrrolidine-, -piperidine and -homopiperidineacetamides and -acetonitriles

INVENTOR(S): Shanklin, James R., Jr.; Wilkinson, James Madison, II.
PATENT ASSIGNEE(S): A. H. Robins Co., Inc., USA

SOURCE: Eur. Pat. Appl., 50 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 178947	A2	19860423	EP 1985-307559	19851018 <--
EP 178947	A3	19870902		
EP 178947	B1	19900926		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
US 4594343	A	19860610	US 1984-662583	19841019 <--
IL 76586	A	19880930	IL 1985-76586	19851004 <--
AU 8548907	A	19860424	AU 1985-48907	19851018 <--
AU 584931	B2	19890608		
CA 1242439	A1	19880927	CA 1985-493333	19851018 <--
AT 56953	T	19901015	AT 1985-307559	19851018 <--
JP 61100563	A	19860519	JP 1985-234392	19851019 <--
US 4812451	A	19890314	US 1986-845148	19860327 <--
US 4812452	A	19890314	US 1986-845170	19860327 <--
US 4810703	A	19890307	US 1986-882743	19860707 <--

PRIORITY APPLN. INFO.: US 1984-662583 A 19841019
EP 1985-307559 A 19851018
US 1986-845148 A1 19860327

OTHER SOURCE(S): CASREACT 105:114918; MARPAT 105:114918

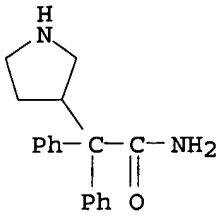
GI For diagram(s), see printed CA Issue.

AB Title compds. I [n = 0-2; p = 0.5; X = O, X; Z = NR1, CH2; Y = CONH2, cyano; Ar1, Ar2 = 2-, 3-, 4-pyrido, (un)substituted Ph; R = H, alkyl; R1-R3 = H, alkyl, (un)substituted Ph, etc.; NR2R3 = heterocyclyl] are prepared as antiarrhythmics. Thus, α,α-diphenyl-3-piperidineacetamide (preparation given) was added to a previously prepared solution of 1,1'-carbonyldiimidazole and H2NCH2CH2NMe2 in DMF, and the resulting mixture refluxed 18 h and worked up to give piperidineacetamide derivative II (40% yield as fumarate, III). At 13 mg/kg i.v. in coronary-ligated dogs, III abolished ectopic ventricular frequency and returned normal sinus rhythm within 2 h. A capsule formulation contained I 10.0, lactose 146.0, and Mg stearate 4.0 mg.

IT 103887-32-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and amidation of)

RN 103887-32-7 CA

CN 3-Pyrrolidineacetamide, α,α-diphenyl- (9CI) (CA INDEX NAME)

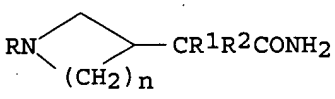


L19 ANSWER 68 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 94:139600 CA
TITLE: Methylenecycloamines
INVENTOR(S): Cale, Albert D., Jr.
PATENT ASSIGNEE(S): A. H. Robins Co., Inc., USA
SOURCE: U.S., 9 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4242261	A	19801230	US 1979-59092	19790719 <--
IL 60375	A	19830731	IL 1980-60375	19800623 <--
ZA 8003778	A	19810930	ZA 1980-3778	19800625 <--
GB 2058049	A	19810408	GB 1980-22967	19800714 <--
GB 2058049	B	19830907		
BE 884357	A1	19801117	BE 1980-201439	19800717 <--
SE 8005235	A	19810120	SE 1980-5235	19800717 <--
SE 448993	B	19870330		
SE 448993	C	19870709		
FR 2461703	A1	19810206	FR 1980-15840	19800717 <--
FR 2461703	B1	19830422		
DE 3027168	A1	19810212	DE 1980-3027168	19800717 <--
DE 3027168	C2	19900705		
DK 8003116	A	19810120	DK 1980-3116	19800718 <--
DK 156653	B	19890918		
DK 156653	C	19900205		
NL 8004165	A	19810121	NL 1980-4165	19800718 <--
AU 8060617	A	19810122	AU 1980-60617	19800718 <--
AU 538138	B2	19840802		
ES 493498	A1	19810701	ES 1980-493498	19800718 <--
CA 1128939	A1	19820803	CA 1980-356552	19800718 <--
HU 29697	A2	19840228	HU 1980-1814	19800718 <--
CH 646954	A5	19841228	CH 1980-5527	19800718 <--
JP 56025153	A	19810310	JP 1980-99273	19800719 <--
JP 01003186	B	19890119		

PRIORITY APPLN. INFO.: JP 1979-90325 A 19790718
US 1979-59092 A 19790719
US 1979-59093 A 19790719

OTHER SOURCE(S): MARPAT 94:139600
GI



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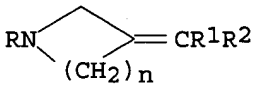


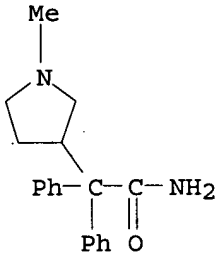
II

AB Amides I (R = alkyl, phenylalkyl, cycloalkyl; n = 1, 2, 3, 4; R1 and R2 are Ph, alkylphenyl) were treated with Br and alkali alkoxides to yield the resp. methylene-substituted compds. II, which exhibited antidepressant activity. I (R = Me, n = 1, R1 = R2 = Ph) was added to Na in MeOH, Br was added at room temperature, and the mixture was stirred 2 h to give II (R = Me, n = 1, R1 = R2 = Ph).

IT 3192-68-5
RL: PROC (Process)
(conversion of, to benzhydrylidene analog)

RN 3192-68-5 CA

CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 69 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 85:123758 CA

TITLE: α,α,α-Trisubstituted acetamides, acetonitriles and methanes

INVENTOR(S): Welstead, William J., Jr.

PATENT ASSIGNEE(S): A. H. Robins Co., Inc., USA

SOURCE: Ger. Offen., 35 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

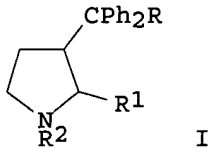
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
DE 2558501	A1	19760708	DE 1975-2558501	19751224	<--
DE 2558501	C2	19870716			
US 4002766	A	19770111	US 1974-536708	19741226	<--
AU 7587549	A	19770623	AU 1975-87549	19751215	<--
AU 498763	B2	19790322			
SE 7514375	A	19760628	SE 1975-14375	19751218	<--
SE 428126	B	19830606			
SE 428126	C	19830915			
FI 7503607	A	19760627	FI 1975-3607	19751219	<--
BE 836974	A1	19760416	BE 1975-163037	19751222	<--
CH 619932	A5	19801031	CH 1975-16604	19751222	<--
DK 7505891	A	19760627	DK 1975-5891	19751223	<--

DK 137751	C	19781009			
NO 7504377	A	19760629	NO 1975-4377	19751223	<--
FR 2295745	A1	19760723	FR 1975-39571	19751223	<--
FR 2295745	B1	19800627			
ZA 7507974	A	19761229	ZA 1975-7974	19751223	<--
GB 1535770	A	19781213	GB 1975-52610	19751223	<--
CA 1055396	A1	19790515	CA 1975-242431	19751223	<--
NL 7515071	A	19760629	NL 1975-15071	19751224	<--
NL 185620	B	19900102			
NL 185620	C	19900601			
ES 443846	A1	19770716	ES 1975-443846	19751224	<--
JP 51091255	A	19760810	JP 1975-159798	19751226	<--
JP 61002658	B	19860127			

PRIORITY APPLN. INFO.: US 1974-536708 A 19741226

GI



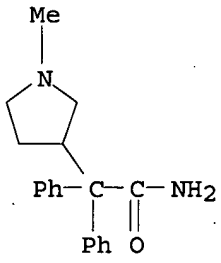
I

AB Pyrrolidineacetonitriles (I; R = CN; R1 = H, Me; R2 = H, Me, Et, Pr, Me2CH, Me2CHCH2, PhCH2, cyclohexyl) are prepared by standard methods. Hydrolysis with concentrated H2SO4 gives the corresponding pyrrolidineacetamides (I; R = CONH2), and reaction with NaNH2 in refluxing PhMe gives 3-benzhydrylpyrrolidines (I; R = H). All I demonstrate antiarrhythmic activity in dogs.

IT 3192-68-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiarrhythmic activity of)

RN 3192-68-5 CA

CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 70 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 63:62947 CA

ORIGINAL REFERENCE NO.: 63:11504c-h,11505a-h,11506a-h,11507a-h

TITLE: 4-(ω-Substituted alkyl)-3,3-disubstituted-1-substituted-2-pyr rolidinones and

4-(ω-substituted alkyl)-3,3-disubstituted-2-pyrrolidinethiones

INVENTOR(S): Lunsford, Carl D.; Cale, Albert D., Jr.
PATENT ASSIGNEE(S): A. H. Robins Co., Inc.
SOURCE: 29 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3192210		19650629	US 1962-237286	19621113 <--

PRIORITY APPLN. INFO.: US 19621113

GI For diagram(s), see printed CA Issue.

AB The title compds. are analeptics, hypotensives, or both. The starting acetonitriles (I) required for the synthesis of the title compds. were prepared as follows. Ph2CHCN (193 g.) was added dropwise at 50° to a stirred suspension of 43 g. NaNH2 in 1 l. dry PhMe, refluxed 4 hrs., treated at a rapid dropwise rate with 162 g. 1-iso-butyl-3-chloropyrrolidine and refluxed with stirring 3 hrs. The cooled mixture was extracted with N HCl and the separated aqueous plus oil layers made basic with NaOH and extracted with Et2O to yield on removal of the Et2O, 250 g. α-(1-isobutyl-3-pyrrolidinyl)-α,α-diphenylacetonitrile (I, A = R = Ph, R1 = iso-Bu) (Ia), b0.15 190-200°, m. 76-7°. The following I nitriles were similarly prepared starting with the appropriate 1-substituted-3-chloropyrrolidine and the selected α,α-acetonitrile (given A, R, R1): allyl, Ph, iso-Pr; C6H11, C6H11, allyl; Me, Me, Ph; PhCH2, Ph, iso-Pr; Ph, 1-iso-Pr-3-pyrrolidinyl, iso-Pr; Ph, 2 (or 3)-thienyl, iso-Pr; p-MeOC6H4, Ph, iso-Pr; m-ClC6H4, Ph, iso-Pr; o-MeC6H4, Ph, iso-Pr; Me, cyclopentyl, iso-Pr; Ph, 2-piperidinyl, Me; Ph, 4-N-methylpiperidinyl; and the 5-Me, 4-Me, 3-Me, and 2-Me derivs. of I (A = R = Ph, R1 = iso-Pr); Ph, Ph, Me, m. 81-2°; Ph, Ph, Et, m. 83-4°; Ph,Ph, iso-Pr, m. 73-4°; Ph, Ph, iso-Bu, m. 76-7°; Ph, Ph, cyclohexyl, b0.005 195-200°; Ph, Ph, MeC6H4, b0.01 215-18°; Ph, pyridyl, MeC6H4, b0.08 200-10°; Ph, pyridyl, iso-Bu, b0.07 161-5°; Ph, pyridyl, cyclohexyl, b0.05 200-8°; Ph, pyridyl, Bu, b0.08 170-5°; Ph, pyridyl, iso-Pr, m. 107-9°; Ph, pyridyl, Et, m. 110-19°; Ph, pyridyl, Me, b0.07 148-51°; p-MeOC6H4, pyridyl, Me, b0.08 170-3°; p-MeOC6H4, pyridyl, Et, b0.08 200-2° p-MeOC6H4, pyridyl, iso-Pr, b0.05 190°; Ph, iso-Pr, Et, b0.15-0Middot;20 121-30°; Ph, Ph, iso-Pr, b0.002 124-5°; Ph, Me, iso-Pr; Ph, cyclopentyl, iso-Pr, b0.005 147-9°; Ph, cyclohexyl, iso-Pr, b0.001 169-75°. The 1,3,3,4-tetra-substituted-2-pyrrolidinones were prepared from the acetonitriles as indicated in the diagram, by first hydrolyzing the nitrile with strong mineral acid at high temperature to give the corresponding acid, and converting the product (II) with an acyl halide to the corresponding mixed anhydride (III). This was rearranged by heating to the 4-(ω-haloalkyl)-2-pyrrolidinone (IV). Thus, a solution of 100 g. Ia in 500 g. 70% H2SO4 was heated 48 hrs. at 130-40°, poured onto ice, made basic with NaOH, extracted with CHCl3, and the CHCl3 solution acidified with HCl, dried, and concentrated The residue was refluxed with 500 ml. SOCl2 hrs. to yield 69 g. 4-(β-chloroethyl)3,3-diphenyl-1-isobutyl-2-pyrrolidinone (IV, Q = Cl, A = R = Ph, R1 = iso-Bu) (IVa), m. 113-13.5°. The following IV derivs. were similarly prepared from the appropriate nitriles (given Q, A, R, R1): Cl, Ph, Ph, PhCH2; Cl, Ph, Ph, Me; Cl, Ph, Ph, cyclohexyl; Cl, Ph, Ph, Et; Cl, Ph, Ph, iso-Pr; Cl, Me,

Ph, iso-Pr. Replacing the SOCl2 with SOBr2 or PBr3 as the halogenating agent yielded the corresponding 4-bromoalkyl compds. Thus, a solution of 31.5 g. of crude α-(1-Et-3-pyrrolidyl)-α,α-diphenylacetic acid-HCl (II, A = R = Ph, R1 = Et) (IIa) (obtained from the nitrile as above) and 20 ml. PBr3 in 70 ml. CHCl3 was refluxed 13 hrs. to yield 4 g. IV (Q = Br, A = R = Ph, R1 = Et), m. 129-30°. A mixture of 2.3 g. α,α-diphenyl-α(1-isopropyl-3-pyrrolidinyl)acetic acid (IIb) and 2.1 g. NaI was refluxed in 25 ml. dry MeCOEt and 2 ml. Ac2O 1.5 hrs. to yield 2.15 g. IV (Q = I, A = R = Ph, R1 = iso-Pr) (IVb), m. 143-6°. A mixture of 25 g. IV (Q = Cl, A = R = Ph, R1 = iso-Pr) (IVc) and 12.5 g. NaI in 200 ml. Me2CO was refluxed 18 hrs. to yield 24.9 g. IVb. A mixture of I (A = R = Ph, R1 = iso-Pr) in 120 g. 70% H2SO4 was heated 64 hrs. at 128-34°, poured into 100 g. ice, made strongly basic with 50% NaOH, the H2O removed in vacuo, and the residue extracted with 2 + 250 ml. boiling EtOH. The residue from the EtOH exts. was dissolved in 400 ml. H2O and treated with AcOH to precipitate 34.1 g. IIb, m. 248-50° (decomposition) (HCONMe2). IIa, m. 136-9° (decomposition) (EtOH-C6H6) was similarly prepared from I (A = R = Ph, R1 = Et).

A suspension of 2.5 g. IIa in 100 ml. dry CHCl3 was treated with dry HCl till solution was complete, 2 ml. SOCl2 added, and the mixture refluxed 2 hrs. to yield 2 g. IV (Q = Cl, A = R = Ph, R1 = Et) (IVd). In the manner of the preceding examples but starting with the appropriate acetonitrile, or the corresponding acid, or intermediate amide, the following IV compds. were prepared (given Q, A, R, R1): Cl, allyl, Ph, iso-Pr; Cl, cyclohexyl, cyclohexyl, allyl; Cl, Me, Me, Ph; Cl, PhCH2, Ph, iso-Pr; Cl, Ph, 1-iso-propyl-3-pyrrolidinyl, iso-Pr; Cl, Ph, 2- or 3-thienyl, iso-Pr; Cl, Ph, 2- or 3-thienyl, iso-Pr; Cl, Ph, p-MeOC6H4, iso-Pr; Cl, Ph, m-ClC6H4, iso-Pr; Cl, Ph, o-MeC6H4, iso-Pr; Cl, Me, cyclopentyl, iso-Pr; CH2Cl, Ph, 2-piperidyl, Me; CH2Cl, Ph, 4-N-methylpiperidyl, iso-Pr; Cl, Ph, Ph, Me; Cl, Ph, Ph, Et; Cl, Ph, Ph, iso-Bu; Cl, Ph, Ph, cyclohexyl; Cl, Ph, Ph, PhCH2; Cl, Ph, 2-pyridyl, PhCH2; Cl, Ph, 2-pyridyl, iso-Bu; Cl, Ph, 2-pyridyl, cyclohexyl; Cl, Ph, 2-pyridyl, Bu; Cl, Ph, 2-pyridyl, iso-Pr; Cl, Ph, 2-pyridyl, Et; Cl, Ph, 2-pyridyl, Me; Cl, p-MeOC6H4, 2-pyridyl, Me; Cl, p-MeOC6H4, 2-pyridyl, Et; Cl, p-MeOC6H4, 2-pyridyl, iso-Pr; Cl, iso-Pr, Ph, Et; Cl, Ph, iso-Pr, iso-Pr; Cl, Me, Ph, iso-Pr; Cl, cyclopentyl, Ph, iso-Pr; Cl, cyclohexyl, Ph, iso-Pr; CH2CH2Cl, Ph, Ph, iso-Pr. In addition the following compds. were also similarly prepared: 4-(γ-chloropropyl)-3-phenyl-3-(2-piperidinyl- 1-methyl-2-pyrrolidinone; 4-(γ-chloropropyl)-3-phenyl-3-[4-(N-methylpiperidinyl)]-1-isopropyl-2-pyrrolidinone; 4-(γ-chloro-2-propyl), 4-(δ-chloro-2-butyl), 4-(γ-chlorobutyl), 4-(γ-chloro-β-methylpropyl), 4-(β-chloropropyl), 4-(β-bromopropyl), 4-(β-chloromethyl)-4-methyl, and 4-(β-chloroethyl)-5-methyl-3,3-diphenyl-1-isopropyl-2-pyrrolidinone.

A solution of 73 g. α- (1 -isopropyl-3-pyrrolidinyl)-α-cyclopentyl-α-phenylacetamide (V, A = Ph, R = cyclopentyl, R1 = iso-Pr) (Va) in 200 ml. AcOH was saturated with HCl and 47.9 g. BuNO2 was added slowly below the surface during 2 hrs. with stirring at 30°. The mixture was kept at room temperature 15 hrs., 3 hrs. at 100° and then concentrated in vacuo. The residue in CHCl3 was washed with H2O and again concentrated in vacuo. This residue was refluxed with 500 ml. SOCl2 2 hrs. to yield 57.3 g. IV (Q = Cl, A = cyclopentyl, R = Ph, R1 = iso-Pr), b0.03 178-80°, m. 74.5-7.5° (ligroine). The following IV compds. were similarly prepared from the corresponding acid amides (given Q, A, R, R1): Cl, iso-Pr, Ph, iso-Pr; Cl, cyclohexyl, Ph, iso-Pr. A solution of 150 g. I (A = cyclopentyl, R = Ph, R1 = iso-Pr) in 800 g. 70% H2SO4 was heated 48 hrs. at 147°, poured onto ice, made basic with 50% NaOH, and extracted with CHCl3 to yield 105 g. Va, b0.2 221-5°. The following

amides were similarly prepared (given A, R, and R1, m.p. (or b.p.): iso-Pr, Ph, iso-Pr, b0.05 175-80°; cyclohexyl, Ph, iso-Pr, b0.14 208-16°; Ph, Ph, Me, 154-5°; Ph, Ph, Et, 141-2°; Ph, Ph, iso-Pr, 141.5-42°; Ph, Ph, cyclohexyl, 119-22°; Ph, 2-pyridyl, Et, 160-1°; Ph, 2-pyridyl, Me, 150-3°; Ph, 2-pyridyl, iso-Pr, 127.5-33°; Ph, 2-pyridyl, Bu, 108-11°. The following IV derivs. were made from I via the amides V, the acids II, followed by rearrangement of the acyl halides (given Q, A, R, R1, m.p.): Cl, Ph, Ph, Me, 140-1°; Cl, Ph, Ph, Et, 117-19°; Br, Ph, Ph, Et, 129-30°; Cl, Ph, Ph, iso-Pr, 106-8°; Cl, Me, Ph, iso-Pr, 102-4°; Cl, Ph, iso-Pr, iso-Pr, 95-6°; Cl, Ph, cyclopentyl, iso-Pr, 74.5-75°; Cl, Ph, cyclohexyl, iso-Pr, 109-11° Cl, Ph, Ph, iso-Bu, 113.5-14.5°; Cl, Ph, Ph, cyclohexyl, 151-2°; Cl, Ph, Ph, PhCH2, 110°; I, Ph, Ph, iso-Pr, 147-9°; CH2Cl, Ph, Ph, iso-Pr, 85-6.5°; Cl, 3-pyridyl, Ph, Et, 100-3°; Cl, Ph, Ph, Et, 150-3°, (side chain CHCH3CH2); Cl, Ph, Ph, Et, 141-2°, (side chain CH2CHCH3). A mixture of 18 g. AcONa and 70 g. IVc in 500 ml. HCONMe2 was refluxed with stirring 15 hrs., partitioned between 500 ml. H2O and 500 ml. CHCl3, and separated to yield from the CHCl3 layer 54 g. IV (Q = OAc, A = R = Ph, R1 = iso-Pr) (IVe), m. 91-4°. A mixture of 2.5 g. IIb and 20 ml. AcOH was refluxed 5 hrs. to yield 1.65 g. IVe. A solution of 34 g. IVe and 4 g. NaOH in 450 ml. EtOH and 10 ml. H2O was refluxed with stirring 1 hr., concentrated in vacuo, and partitioned between CHCl3 and H2O to yield from the CHCl3 layer 22 g. IV (Q = OH, A = R = Ph, R1 = iso-Pr),m. 180-2°(aq.EtOH). A solution of 16.2 g. NaHS.2H2O and 30 g. IVc in 400 ml. 85% EtOH was refluxed 7 hrs., concentrated, and the residue partitioned between CHCl3 and H2O to yield from the CHCl3 layer 17 g. IV (Q = SH, A = R = Ph, R1 = iso-Pr) (IVf), b0.5 220-30°, m. 104-7° (EtOH-H2O). A solution of 11.5 g. MeBr in 200 ml. EtOH was added to a solution of 20 g. IVf in 200 ml. EtOH containing 1.5 g. Na and stirred at room temperature 4 hrs. to yield 20 g. IV (Q = SMe, A = R = Ph, R1 = iso-Pr),m. 123-5°. A solution of 34g. IVc in 200 ml. absolute EtOH containing 2.5 g. Na was heated in a closed system 16 hrs. at 140° to yield 27.5 g. IV (Q = OMe, A = R = Ph, R1 = iso-Pr), m. 105-6° (MeOH-H2O). PhONa (prepared from 8.3 g. PhOH and 2 g. Na in 300 ml. EtOH) and 30 g. IVc in 100 ml. EtOH was refluxed for 7 hrs. to yield 17 g. IV (Q = OPh, A = R = Ph, R1 = iso-Pr), m. 104-6° (EtOH-H2O). A solution of 25 g. IVc, 25 g. KBr, and 60 ml. 48% HBr in 250 ml. AcOH was refluxed with stirring 2 hrs., treated with 60 g. Zn dust in small portions, then with 60 ml. 48% HBr (dropwise during 2 hrs.), and allowed to stand overnight at room temperature to yield 9 g. IV (Q = H, A = R = Ph, R1 = iso-Pr), m. 95-7° (aqueous EtOH). The corresponding R1 = iso-Bu compound, m. 94.0-6.5° was similarly prepared from IVa. In the manner of the preceding examples, the complete list of ω-chloroalkyl compds. given above were converted to the corresponding ω-hydroxyalkyl compds. and 4-ω-acyloxyalkyl compds. The following are representative of this group of compds. (given Q, A, R, R1, and m.p.): OAc, Ph, Ph, iso-Pr, 91-4°; SH, Ph, Ph, iso-Pr, 104-7°; SMe, Ph, Ph, iso-Pr, 123-5°; OMe, Ph, Ph, iso-Bu, 86-7°; OMe, Ph, Ph, iso-Pr, 105-6°; PhO, Ph, Ph, iso-Pr, 104-6°; OH, Ph, Ph, iso-Pr, 180-2°; CH2OH, Ph, Ph, iso-Pr, 142-3°; o-MeOC6H4, Ph, Ph, iso-Pr, 135-7°; CO2C5H4N, Ph, Ph, iso-Pr, 104-5°; o-HOC4H4CO2, Ph, Ph, iso-Pr, 111-12°. A mixture of 342 g. IVc and 75 g. NaCN in 1 l. HCONMe2 was heated with stirring 4 hrs. at 100° and poured into ice-H2O to yield 288 g. IV (Q = CN, A = R = Ph, R1 = iso-Pr) (IVg), m. 150-1°. A mixture of 94 g. IVg and 500 ml. 70% H2SO4 was

heated with stirring 24 hrs. at 80-90° and poured into ice-H2O to yield 93% IV (Q = CO2H, A = R = Ph, R1 = iso-Pr) (IVh), m. 175-6°. A suspension of 144 g. IVh in 500 ml. dry C6H6 was treated at 20-5° with 97.5 g. SOCl2 and refluxed 1 hr. to yield IV (Q = COCl, A = R = Ph, R1 = iso-Pr) (IVi), m. 141.5-3.5°. A solution of 30 g. IVi in 300 ml. dry EtOH was added to a solution of 2.05 g. Na in 200 ml. EtOH and stirred overnight at room temperature to yield 23 g. of the ester IV (Q = CO2Et, A = R =

Ph, R1 = iso-Pr) (IVj), m. 84-5° (70% MeOH). IVi (54 g.) was added portionwise with vigorous stirring to cold concentrated NH4OH to yield 46 g. IV(Q = CONH2, A = R = Ph, R1 = iso-Pr), m. 203.5-5.0°. A solution of 7.75 g. MeNH2 in 150 ml. C6H6 was added dropwise with stirring to a suspension of 25 g. IVi in C6H66 and refluxed 1 hr. to yield 84% IV (Q = CONHMe, A = R = Ph, R1 = iso-Pr), m. 170-1°. IV (Q = CONMe2, A = R = Ph, R1 = iso-Pr), m. 149-50° was similarly prepared A mixture of 10 g. CdCl2 and Grignard reagent (prepared from 10.9 g. EtBr and 2.4 g. Mg in 100 ml. dry Et2O) was refluxed 1 hr., the Et2O distilled, 200 ml. dry PhMe added the solution heated 30 min. at 90°, cooled to 60° , a solution of 30 g. IVi in 150 ml. PhMe added dropwise, the mixture stirred 2 hrs. at 85° and hydrolyzed with H2O and 6N HCl, the PhMe layer washed with dilute NaOH, dried, and distilled to yield 8 g. IV (Q = COCH2CH3, A = R = Ph, R1 = iso-Pr), b0.2 220-50° m. 120-2.5°, (60% EtOH). To a boiling solution of 5 g. IVj in 50 ml. absolute EtOH was added as rapidly as possible 2 g. Na and the mixture heated to reflux; 30 ml. H2O was added, the mixture refluxed 1 hr., and the solvent removed to yield IV (Q = CH2OH, A = R = Ph, R1 = iso-Pr) (IVk), m. 140-1.5° (50% EtOH). To a suspension of 10 g. NaBH4 was added rapidly with stirring 25 g. IVi in 200 ml. dry dioxane and the mixture refluxed 4 hrs. to yield 10 g. IVk. A solution of 7.4 g. SOCl2 in 50 ml. CHCl3 was added dropwise to a solution of 10.5 g. IVk and 4.9 g. C5H5N in 100 ml. CHCl3 with stirring and ice bath cooling. The mixture was refluxed 5 hrs., cooled, and treated with 50 ml. 3N HCl to yield 8 g. IV (Q = CH2Cl, A = R = Ph, R1 = iso-Pr) (IVl), m. 85.0-6.5° (60% EtOH). A mixture of 3.9 g. NaCN and 9.2 g. IVl in 100 ml. HCONMe2 was refluxed for 17 hrs. to yield 5 g. IV (Q = CH2CN, A = R = Ph, R1 = iso-Pr), m. 126-7° (iso-PrOH). The list of 4-(ω-haloalkyl)-2-pyrrolidinones given previously were converted in the manner of the preceding examples to the nitriles, acids, acid halides, acid esters, and acid amides. The following representative compds. of this group were also thus prepared (R = A = Ph, R1, and m.p. given): CN, iso-Pr, 150.5-1.0°; CO2H, iso-Pr, 175-6°; CONMe3, iso-Pr, 149-50°; CONH2, iso-Pr, 203.5-5.0°; CONHMe, iso-Pr, 170-1°; hexamethyteniminocarbonyl, iso-Pr, 144-5°; N-pyrrolidinocarbonyl, iso-Pr, 179.5-80°; CO2Et, iso-Pr, 84-5°; CH2CN, iso-Pr, 126-7°; CONHC4H9, iso-Pr, 113.5-14°; morpholinocarbonyl, iso-Pr, 157.5-8.5°; COEt, iso-Pr, 120-2.5°; CN, Et, 177-80°. A solution of 40 g. IVd and 11 g. Me2NH in 250 ml. EtOH was heated 16 hrs. at 100° in a scaled system and concentrated in vacuo to yield 32 g. IV.HCl.H2O (Q = NMe2, A = R = Ph, R11 = Et), m. 162-6°. The following amines were similarly prepared and isolated as the indicated HCl or HCl.H2O salts (given Q, A, R, R1 for structure IV): NMe2, Ph, Ph, iso-Bu (HCl) (IVm.HCl); NMe2, Ph, Ph, PhCH2 (HCl.H2O); 2-pyrrolidinoethyl, Ph, Ph, Et (HCl.H2O); NHMe, Ph, Ph, iso-Pr (HCl); 4-methyl-1-piperazino, Ph, Ph, iso-Pr (2HCl.2H2O); 4-phenyl-1-piperazino, Ph, Ph, iso-Pr (HCl.2H2O); morpholino, Ph, Ph, iso-Pr (HCl.H2O); 2,6-dimethylmorpholino, Ph, Ph, iso-Pr (maleate); 4-carbomethoxy-1-piperazino, Ph, Ph, iso-Pr (HCl.2H2O); 2-morpholino, Ph, Ph, Et, (HCl.H2O m. 217-19°); 2-piperidino, Ph, Ph, Et; NBu2, Ph, Ph, Et, b0.05 205-10°; NMe2, Ph, cyclopentyl, Et; 2-(3,5-dimethylmorpholino), Ph, Ph, iso-Pr (maleate m. 149-50°, fumarate m. 200-3°); 2-(2,6-dimethylmorpholino), Ph, Ph, iso-Pr

(maleate, m. 177-8°). Various maleates and fumarates of the above compds. were similarly prepared IVm.HCl (10 g.) was partitioned between CHCl3 and dilute NH4OH. The CHCl3 layer was concentrated, the residue dissolved in MeCOEt, refluxed, treated with 4.75 g. MeBr in MeCOEt, and cooled to yield 11.5 g. IVm methobromide, m. 218-19° (MeCOEt). A solution of 25 g. IV (Q = CN, A = R = Ph, R1 = iso-Pr) and 2 teaspoonsfuls of Raney Ni in 300 ml. absolute EtOH was shaken in a H atmospheric to yield 13 g. product b0.2 210-15°, which was treated with 5 g. fumaric acid to yield 6.5 g. IV fumarate (Q = CH2NH2, A = R = Ph, R1 = iso-Pr), m. 149-52°. The list of 4-ω-haloalkyl-2-pyrrolidinones given previously were converted in the manner of the preceding examples to the corresponding 4-ω-aminoalkyl-, and 4-ω-morpholinoalkyl-2-pyrrolidinones. The following representative compds. of this group were thus prepared (structure IV, R = Ph; Q, A, R1, salt, and m.p. given): NMe2, Ph, Et, HCl.H2O, 161-4°; NBu2, Ph, Et, --, -- (b0.05 205-10°); pyrrolidino, Ph, Et, HCl.H2O, 169-72°; piperidino, Ph, Et, --, 89°; CH2NH2, Ph, iso-Pr, fumarate, 149-52°; NHMe, Ph, iso-Pr, HCl,237-9°; N-methylpiperazino, Ph, iso-Pr, 2HCl.2H2O, 185-9°; N-phenyl-piperazino, Ph, iso-Pr, HCl.2H2O, 145-51°; NMe2, Ph, iso-Bu, HCl, 154-5°; NMe2, Ph, iso-Bu, MeBr, 218-19°; NMe2, Ph, PhCH2, HCl.H2O, 181-3°; NMe2, Ph, iso-Pr, --, 94-8.5°; NEt2, Ph, iso-Pr, fumarate, 156-9°; NMe2, iso-Pr, iso-Pr, HCl, 208-10°; hexamethylenimino, Ph, iso-Pr, fumarate, 163-5°; N(Me)COMe, Ph, iso-Pr, --, 120-1°; phthalimido, Ph, iso-Pr, --, 164-6°; morpholino, Ph, Et, HCl.H2O, 217-19°; morpholino, Ph, iso-Pr, HCl.H2O, 182-5°; 2,6-dimethylmorpholino, Ph, iso-Pr, maleate, 177-8°; morpholino, Ph, iso-Pr, maleate, 173-7°; 3,5-dimethylmorpholino, Ph, iso-Pr, maleate, 149-50°; 3,5-dimethylmorpholino, Ph, iso-Pr, fumarate, 200-3°; morpholino, iso-Pr, iso-Pr, HCl, 173-6°; morpholino, Ph, iso-Pr, maleate, 155°; thiomorpholino, Ph, iso-Pr, HCl.H2O, 225-30° (decomposition); CH2NHCOMe, Ph, iso-Pr, --, 113-15°; NHCH2CH:CH2, Ph, iso-Pr, --, 103-5°; NH2, Ph, iso-Pr, --, 102-3.5°; morpholino, Ph, Me, --, 130-1°; morpholino, Ph, Et, benzoate, 123-4°; NMe2, Ph, Et, HCl,251-3° morpholino, Ph, Et, HCl,255-61.5°. The 4-(ω-haloalkyl)-3,3-disubstituted-1-substituted-2-pyrrolidinethiones (VI) corresponding to the 2-pyrrolidinones IV were prepared by reacting the latter with P2S5. Thus, a mixture of 150 g. IVc, 23.3 g. P2S5, and 25 g. K2S in 700 ml. dry PhMe was refluxed with stirring 24 hrs. to yield VI (Q = Cl, A = R = Ph, R1 = iso-Pr) (VIa), m. 149-51° (PhMe).

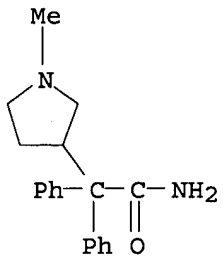
The following VI compds. were similarly prepared (given Q, A, R, R1): Cl, Ph, Ph, Et; Cl, Ph, Ph, Me; Br, Ph, Ph, Et; CN, Ph, Ph, iso-Pr, m. 166-7° (iso-PrOH); CN, Ph, Ph, Et; CN, Ph, Ph, Me; CN, Ph, Ph, cyclohexyl. A solution of 25 g. VIa in 100 ml. morpholine was refluxed 18 hrs. to yield VI.HCl (Q = morpholino, A = R = Ph, R1 = iso-Pr), m. 275°. The corresponding Q = Et, and Q = Me compds. were prepared similarly. Following the procedures given above for the IV compds., the following corresponding VI compds. were similarly prepared (given Q, A, R, R1): NMe2, Ph, Ph, iso-Pr (HCl.H2O salt), m. 196-7°; methyl-1-piperazino, Ph, Ph, iso-Pr, m. 133-4°; pyrrolidino, Ph, Ph, Et; thiomorpholino, Ph, Ph, iso-Pr; NEt2, Ph, Ph, iso-Pr (HCl salt); CO2H, Ph, Ph, iso-Pr, m. 191-4°; CO2H, Ph, Ph, Et; CO2H, Ph, Ph, Me; CO2H, Ph, Ph, cyclohexyl; COCl, Ph, Ph, iso-Pr; CO2Et, Ph, Ph, iso-Pr, m. 148.5-51°; COCl, Ph, Ph, Et; CO2Et, Ph, Ph, Et; CO2Me, Ph, Ph, Me; CO2Pr, Ph, Ph, iso-Pr; CONMe2, Ph, Ph, iso-Pr, m. 109-11°; CONEt2, Ph, Ph, Et; CONHMe, Ph, Ph, Me; CONHBu, Ph, Ph, iso-Pr; OH, Ph, Ph, iso-Pr; OH, Ph, Ph, Et; OH, Ph, Ph, Me; CO2Me, Ph, Ph, iso-Pr; CO2Et, Ph, Ph, Me; CO2Et, Ph, Ph, Et; SH, Ph, Ph, iso-Pr, b0.01 200-10°;

SMe, Ph, Ph, iso-Pr; MeO, Ph, Ph, iso-Pr; MeO, Ph, Ph, iso-Bu; BzO, Ph, Ph, iso-Pr; 3-dimethylaminophenoxy, Ph, Ph, iso-Pr, m. 104-6°; COCH2CH3, Ph, Ph, iso-Pr; N-acetyl-N-methylamino, Ph, Ph, Me. Formulations are given for the preparation of capsules, tablets, and injectable solns.

IT 3192-68-5P, 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl-
RL: PREP (Preparation)
(preparation of)

RN 3192-68-5 CA

CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 71 OF 73 CA COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 63:62946 CA

ORIGINAL REFERENCE NO.: 63:11504b-c

TITLE: 4-(ω-Substituted alkyl)-3,3-disubstituted-1-substituted-2-pyrrolidinones and 4-(ω-substituted alkyl)-3,3-disubstituted-1-substituted-2-pyrrolidinethiones

INVENTOR(S): Lunsford, Carl D.; Cale, Albert D., Jr.

PATENT ASSIGNEE(S): A. H. Robins Co., Inc.

SOURCE: 30 pp.

DOCUMENT TYPE: Patent

LANGUAGE: Unavailable

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3192221		19650629	US 1961-156945	19611204 <--

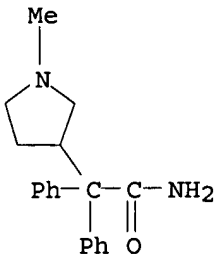
PRIORITY APPLN. INFO.: US 19611204

AB The acetonitrile intermediates required for the synthesis of the title compds. were prepared as in U.S. 3,192,210 (following abstract). The examples are also the same as in the latter but the claims are different.

IT 3192-68-5P, 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl-
RL: PREP (Preparation)
(preparation of)

RN 3192-68-5 CA

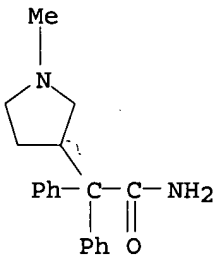
CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 72 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 63:62945 CA
ORIGINAL REFERENCE NO.: 63:11504b
TITLE: 1,3,3-Trisubstituted-4-(β-haloalkyl)-2-pyrrolidinone
INVENTOR(S): Lunsford, Carl D.; Cale, Albert D., Jr.
PATENT ASSIGNEE(S): A. H. Robins Co., Inc.
SOURCE: 24 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3192230		19650629	US 1961-88036	19610209 <--
PRIORITY APPLN. INFO.:			US	19610209

OTHER SOURCE(S): MARPAT 63:62945
AB The acetonitrile intermediates required for the synthesis of the title compds. were prepared as in U.S. 3,192,210 (preceding abstract). The examples are also the same as in the latter but the claims are different.
IT 3192-68-5P, 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl-
RL: PREP (Preparation)
(preparation of)
RN 3192-68-5 CA
CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



L19 ANSWER 73 OF 73 CA COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 58:3241 CA
ORIGINAL REFERENCE NO.: 58:508e-f
TITLE: N-Alkylation of indoles
INVENTOR(S): Lind, Charles J.; Sogn, Allen W.
PATENT ASSIGNEE(S): Allied Chemical Corp.

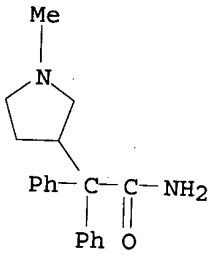
SOURCE: 4 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3012040		19611205	US 1958-767289	19581015 <--
PRIORITY APPLN. INFO.:			US	19581015

AB A mixture of 1580 parts PhCl and 1150 parts aqueous paste containing 633 parts 2-phenyl-3-indolecarboxaldehyde (2.86 mol) was stirred 10-15 min. to a uniform slurry. The agitated slurry was then treated slowly with 2290 parts 49.9°Be. aqueous caustic soda (28.6 mol NaOH) and heated to 60-2° over a period of 20 min., with the temperature maintained by cooling and heating. Me2SO4 595 parts was added in 45 min. and stirred an addnl. 45 min. The mixture was drowned in 1450 parts cold H2O (10-20°) over a period of 45 min., steam distilled to remove PhCl, the residue was cooled, filtered, washed with 8000 parts cold H2O, and dried at 60-5° to give 662 parts of 1-methyl-2-phenyl-3-indolecarboxaldehyde, m. 125-6°. Similarly prepared were: 1-methyl-2-phenylindole, 97.5% from 2-phenylindole, and theor. yield of 1,2,3-trimethylindole by fractional distillation of the oil layer after removal of PhCl by steam distillation

IT 3192-68-5P, 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl-
RL: PREP (Preparation)
(preparation of)

RN 3192-68-5 CA
CN 3-Pyrrolidineacetamide, 1-methyl-α,α-diphenyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



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L4 STRUCTURE UPLOADED
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L6 STRUCTURE UPLOADED
L7 146 S L6 FULL

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L13            0 S L12 NOT L7
L14              STRUCTURE UPLOADED
L15          815 S L14 FULL
L16          669 S L15 NOT L7

     FILE 'CA' ENTERED AT 12:47:44 ON 24 JAN 2007
L17          139 S L16
L18          138 S L17 NOT L8
L19           73 S L18 AND PY<2004

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

STN INTERNATIONAL LOGOFF AT 12:48:55 ON 24 JAN 2007
```